Functional and structural aspects of tracheoesophageal voice prostheses

Leunisse, Casper

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FUNCTIONAL AND STRUCTURAL ASPECTS OF TRACHEOESOPHAGEAL VOICE PROSTHESES

Stellingen
behorende bij het proefschrift

'Functional and structural aspects of tracheoesophageal voice prostheses'

C. Leunisse

Groningen, 13 december 2000

1.

Bij experimenteel onderzoek met tracheo-eosofageale spraakprothesen moet gestreefd worden naar laboratoriumomstandigheden, die de klinische situatie zoveel mogelijk benaderen.

(dit proefschrift)

2.

De kunstkeel is zeer bruikbaar om bepaalde invloeden op tracheo-oesofageale spraakprothesen te testen alvorens complexe en tijdrovende prospectieve patiënt-gecontroleerde studies uit te voeren.

(dit proefschrift)

3.

In een tijd waarin de gezondheidszorg gebudgetteerd is, kan ook de kostprijs van een tracheo-oesofageale spraakprothese een rol spelen in de keuze van het type prothese. Maar uiteindelijk moet de patiënt kunnen bepalen welke prothese voor hem of haar de meest ideale is.

4.

Voordat een tracheo-oesofageale spraakprothesen commercieel beschikbaar komt, is fundamenteel onderzoek gevolgd door een klinische evaluatie essentieel

5.

Een concreet voorbeeld van de uitdrukking "de wonderen zijn nog niet de wereld uit" is dit proefschrift.

6.

Een ideale relatie is op voorhand met topsporters mogelijk; zij schijnen alles te slikken.

7.

De veranderde positie van de arts in de maatschappij heeft vele voordelen. Het feit dat een arts bij mogelijk gemaakte fouten met naam en toenaam in de media wordt genoemd is hier echter een bedenkelijk voortvloeisel van.

8.

Het indienen van schadeclaims bij de tabaksindustrie door mensen met ernstig longlijden is een vorm van mosterd na de maaltijd, en getuigt bovendien van onverantwoordelijk gedrag.

9.

Als het gezin de hoeksteen van de samenleving is, dan moet de oorsprong van maatschappelijke excessen zoals onverdraagzaamheid, zinloos geweld etc. bij het gezin gezocht worden.

10.

De wet arbeidsongeschiktheid (WAO) houdt meer mensen bezig dan ze aan het werk houdt.

11.

Een trap in de lucht is een vorm van zinloos geweld. (Thomas Acda)

RIJKSUNIVERSITEIT GRONINGEN

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Aan mijn ouders,
voor Hanneke, Bram en Willemijn

Contents

Chapter 1

GENERAL INTRODUCTION

General introduction

Although head and neck tumours are rather rare malignancies, the treatment of this disease can have major consequences for the patient. Especially total laryngectomy for advanced laryngeal or pharyngeal carcinoma or recurrences after radiotherapy can provide serious physical and psychosocial problems. Of these problems the loss of speech is considered to be one of the most disabling consequences. From the first laryngectomy in 1873 voice rehabilitation has been a considerable concern.[1] Of all the introduced speech rehabilitation methods electromechanical speech, esophageal speech, and tracheo-esophageal shunt speech are the most suitable. In the shunt method, which is basically a modification of the method described by Guttman in 1931, expiratory air is used as energy source.[2] The occurrence of aspiration (of saliva, fluid and food substances) as well as secondary stenosis of the tracheo-esophageal fistula were the key complications of all tracheo-esophageal shunt modifications. To overcome these problems Singer and Blom introduced a endoscopic technique in which a silicone tracheoesophageal one-way (duck-bill) valve was inserted following laryngectomy.[3] Fluent speech results were obtained after insertion of the voice prostheses as a secondary procedure. After the introduction of this device several types of silicone voice prostheses have been introduced with good results.[4-7] Specific modifications of the silicone prosthesis were designed to establish more effortless speech and fluent phonation by improving aerodynamic properties of the valve, sufficient retaining properties to allow primary and secondary insertion, acceptable device life, easy maintenance procedures and simple replacement techniques in the outpatient clinic. The silicone voice prostheses can be divided into the non-indwelling voice prostheses and the indwelling voice prostheses. The non-indwelling types can only be inserted after a patent fistula has been developed, whereas the indwelling types can be inserted by a primary as well as a secondary procedure. The non-indwelling voice prostheses can be removed and replaced by the patient for cleansing. The indwelling types have self-retaining capacities with respect to the tracheoesophageal fistula. One of the main drawbacks of the indwelling silicone voice prosthesis is the limited average in *situ* lifetime of 3-5 months.[8,9] These devices must be replaced by a

physician using specially manufactured instruments. Although this procedure can be done under local anaesthesia on an outpatient basis, it can still be considered an inconvenient procedure for the patient. The most frequently reported reasons for replacement are leakage of salivary or food through the prosthesis and increased effort to speech resulting in impaired speech quality. Deterioration of the prosthesis caused by microbial colonization and biofilm formation of the silicone material is regarded to be responsible for these limitations.[10,11] The biofilm isolated from failed voice prostheses usually consists of a variety of bacteria and yeasts originating from the oral cavity and skin flora. In this process of biofilm formation and deterioration of silicone voice prostheses bacterial colonisation seems to be essential for the adhesion of more invasive *Candida* species.[12-16]

Objectives of this study

Nowadays voice prosthesis assisted tracheo-esophageal speech is the standard in post-laryngectomy voice rehabilitation in Western Europe and many other parts of the world. Although the silicone tracheoesophageal voice prostheses have undergone important changes since the introduction of the first valve prosthesis, the major disadvantage of these prostheses (limited in *situ* life time) has not been changed. The limited *in situ* life time is strongly related to biofilm formation on the silicone material of the devices and shows considerable variation between different types of prostheses.
In this study a comparison of different indwelling low resistance tracheo-esophageal voice prostheses was made by investigating the functional related difficulties and structural characteristics of these prostheses. Standardized in *vitro* methods were developed to overcome the specific problems of patient controlled studies. With these methods aerodynamic features and biofilm formation of voice prostheses can be explored. The aim of this study was to come to a comprehensive analysis of tracheo-esophageal shunt prostheses related problems which can finally attribute to improved speech rehabilitation after total laryngectomy.

Chapter 2 presents an introduction including a retrospection and an overview of several aspects of total laryngectomy and the different methods of vocal rehabilitation after total laryngectomy.

In Chapter 3 a retrospective analysis of the *in situ* life time of the Groningen Low Resistance and the Provox 2 voice prostheses used in the Department of Otorhinolaryngology of the University Hospital Groningen is described. This comparison is based on 712 voice prostheses replacements at 102 patients after total laryngectomy.

In Chapter 4 a customized experimental setup for determining aerodynamic properties of tracheoesophageal voice prostheses is described. Determination and a comparison of the aerodynamic characteristics of six different low resistance silicone voice prostheses is performed under laboratory conditions imitating the *in vivo* conditions as close as possible.

In Chapter 5 an *in vitro* model, the artificial throat, is introduced. The artificial throat is developed in order to simulate the natural process of biofilm formation under dynamic nutrient conditions with subsequent assessment of functional and morphological aspects of silicone voice prostheses.

In Chapter 6 biofilm formation on different silicone tracheoesophageal voice prostheses in the artificial throat was allowed to develop. The morphological changes of the valve system during this biofilm formation subject of study. This was done in order to explore the mechanical features which may explain the differences in device life between the current most used voice prostheses.

In Chapter 7 the influence of buttermilk on the biofilm formation on silicone rubber voice prosthesis under *in vitro* conditions is studied in the artificial throat. Clinical observations of laryngectomized patients suggested that consumption of buttermilk prolongs the life-time of indwelling silicone rubber voice prostheses.

In Chapter 8 the results of the investigations presented in the previous chapters are summarized. The importance of the analysis of functional and structural characteristics of each tracheoesophageal shunt prosthesis is emphasized and recommendations with regard to future research on this subject are presented.

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Chapter 2

VOICE REHABILITATION AFTER TOTAL LARYNGECTOMY: AN OVERVIEW

Introduction

In general, head and neck tumors comprise all benign, premalignant and malignant tumors originating from the mucous membrane of the upper aerodigestive tract and salivary glands. In comparison to the incidence of other tumor sites, tumors of the head and neck are rather rare. The Dutch Cancer registry recorded that only 4 % of all the newly diagnosed malignancies in a year comprised head and neck tumors.[1] Carcinoma of the larynx has a reported incidence of approximately 30 - 40 % and is the most occurring head and neck tumor. In fact it is not the incidence of head and neck tumors causing major concern, but more the sequels resulting from specific treatments. Depending on the tumor stage, treatment with curative intent may vary between radiotherapy alone and combined treatment modalities which may cause severe mutilation and disturbances in the head and neck region.

Laryngeal cancer

In 1996, 700 new cases of laryngeal cancer were reported in the Netherlands.[2] Approximately 85 -90% of the laryngeal cancers are squamous cell carcinomas originating from the laryngeal mucous membranes. In accordance with most head and neck malignancies, the incidence of laryngeal cancer grows with increasing age with a preferential age between 50 and 70 years for men and 5-10 years earlier in women. Malignant tumors of the larynx still occur more often in men than in women. However, the incidence of laryngeal cancer in women is increasing probably due to altered consumption pattern (particularly smoking habits). This has resulted in a changed men to women ratio for laryngeal cancer in the Netherlands from 1:23 to 1:8 in 1972 and 1992, respectively.[1] Tobacco use, especially in case of long-lasting and excessive consumption, is an important etiological factor in developing laryngeal cancer.[3] A synergistic effect between smoking and alcohol consumption is assumed in cases of supraglottic laryngeal cancer. Continuation of both smoking and drinking habits by patients may increase the risk of a second primary tumor.[4] It is also related with an increased morbidity of the treat-

ment and has a reverse influence on the outcome of treatment.[5] In general, malignancies of the true vocal cords or glottis are the most common (66 %) followed by supraglottic cancers. The prevalence of subglottic cancers is low. The most common symptom of glottic cancer is hoarseness in an early stage, while dysphagia can be a presenting symptom of supraglottic malignancies. Late symptoms of laryngeal cancers are dyspnea, stridor (as a consequence of laryngeal obstruction) and referred pain. Lymphogenic spread to cervical lymph nodes is unusual in glottic cancer, but more frequently diagnosed in case of supraglottic cancers. Haematogenic metastases occur rarely to the lungs. Laryngeal carcinoma has a rather favourable prognosis, with an overall five years survival of 65 %.[6] Although, the extent of the tumour and lymphogenic spread to cervical lymph nodes will ultimately determine the prognosis.

The various treatment modalities of laryngeal carcinoma consist of carbon dioxide laser evaporation of small glottic tumors, radiotherapy, partial or total surgical removal of the larynx or a combination of these modalities. The treatment of choice depends on the stage of the disease. In general the small tumors can be treated by radiotherapy, while in the more advanced stages a surgical approach is advocated followed by radiotherapy.

Total laryngectomy

A total laryngectomy is the most common surgical treatment for advanced laryngeal cancer and in case of recurrence after initial radiotherapy. By removing the entire larynx, from hyoid bone up to the uppermost tracheal rings, a complete separation between the pharynx and trachea is created. The resulting defect of the pharynx anteriorly is closed and covered by approximating layers of pharyngeal and strap muscles. The remaining trachea is sutured into the skin of the neck (Fig. 1a and 1b). A concomitant neck dissection in case of lymphogenic metastasis can be performed.

Figure 1a *Figure 1b*

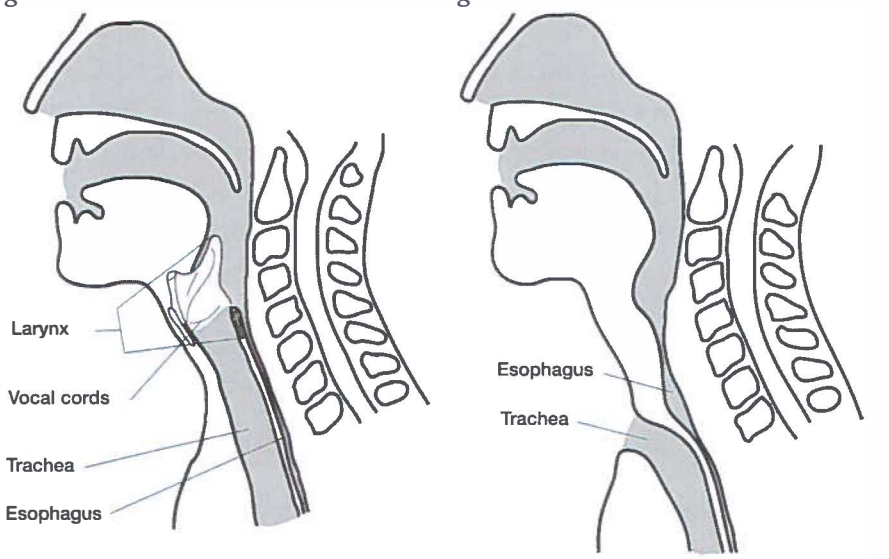

Figure 1. Schematic drawing of the anatomy before and after laryngectomy. In the preoperative situation (a) there is no seperation of the respiratory and digestive tract as is seen postoperatively (b). After laryngectomy respiration take place trough a tracheostoma.

The result of a laryngectomy is not limited to the loss of the larynx and its vocal folds, the lower respiratory tract is separated from the vocal tract as well as from the upper digestive tract. Breathing is performed through the created tracheostoma and there is no connection between the oral cavity and the airways (Fig.1a and b). Therefore surgical removal of the larynx has radical consequences for the patients. It will seriously affect major laryngeal functions e.g. phonation, airway control, swallowing, effort closure during strenuous activity, sense of smell (and taste) and coughing.[7,8] Beside these physical changes, patients suffer often from psychological and social pro-blems.[9] The loss of normal vocal function plays a major role in this psychological distress. As a consequence much attention has been paid to vocal rehabilitation after total laryngectomy throughout the years. In the following section of this chapter different methods of voice rehabilitation after laryngectomy will be discussed.

Methods of voice rehabilitation after total laryngectomy

The loss of vocal function is generally considered to be the most disabling consequence of a total laryngectomy. This was already recognized when the first laryngectomy was performed by Billroth in 1874.[10] At that time successful voice restoration was achieved with an artificial device. This was the first documented use of an artificial larynx. The device in question constituted of a canula which shunted air from the tracheostoma to a pharyngostoma. This canula consisted of a phonatory part where sound was produced by airflow passing through a vibrating metal membrane. This device was also capable of preventing aspiration from the pharyngostoma by a trapdoor flap which closed with swallowing and opened for speech. The rehabilitated voice was loud and clear though monotonous.[11] Inspired by this success several other devices were developed at the end of the 19th century.[12-14] Not very long after the first laryngectomy this technique was modified by primary closure to overcome the troublesome pharyngostoma.[15,16] As a consequence voice restoration by using shunt prostheses was abolished and esophageal speech was introduced. The high mortality rate after total laryngectomy in those early years and the introduction of radiotherapy around 1900 reduced the number of executed laryngectomies.[17] These developments had resulted in a diminished use of artificial laryngeal devices in the following years.

In the twentieth century, Guttman is seen as a pioneer of surgical voice restoration. In 1932, he reported on the use of a fistula between trachea and esophagus executed by one of his patients with a diathermic needle.[18] With this procedure shunting of pulmonary air from the airways to the esophagus and pharynx was established, where sound was elicited. However, spontaneous closure of the fistula allowed only temporary vocal rehabilitation. In later years, efforts to prevent leakage or stenosis of the surgical tracheoesophageal fistula have led several surgeons to introduce surgical techniques to overcome these problems. Attempts of Conley to abort these problems with his autogenous vein graft fistulization procedure were not successful.[19,20] To establish an internal tracheoesophageal shunt, a three-stage method was proposed by Asai in 1965.[21,22] Although this technique was modified several times, aspiration problems, shunt disruption and stenosis of the shunt were

encountered.[23-27] Four years later Staffieri introduced a surgical shunt method called "Neoglottis Phonatoria" for its resemblance to the glottis.[11,28-30] A small slit in the anterior pharyngoesophageal wall of the laryngectomized patient was created. Formation of a valve that linked the trachea to the pharynx a part of of the esophageal wall was placed over the top of the trachea. Although successful phonation in the majority of the cases was reported [31-33], this technique was often complicated by severe chronic aspiration, shunt stenosis and recurrence of the tumor.[11,28,32,34,35] Amatsu and colleagues introduced a tracheoesophageal shunt in 1977, which was modified in 1986.[36-38] With this technique a tracheal mucosal flap from the posterior tracheal wall was created and this was tunnelled over a tracheoesophageal side-to-side anastomosis. Nevertheless the same problems of stenosis and aspiration were encountered. Many other efforts have been explored to accomplish an effective cancer control with avoidance of aspiration through the shunt and stenosis of the fistula.[39-41] In general surgical voice restoration with tracheoesophageal shunt methods resulted in good voice quality, but aspiration through the shunt and stenosis of the fistula remained as the major drawbacks.[42]

In order to overcome the problems associated with the above described unprotected shunting techniques, development of a prosthetic devices that prevented stenosis and leakage was the aim. In 1972 Mozolewski described the first real tracheoesophageal valved voice prosthesis.[43] But, in 1979 a new era of prosthetic vocal rehabilitation after total laryngectomy began, with the introduction of the commercially available "duckbill" voice prosthesis by Blom and Singer.[44]

At this moment the three most suitable methods of postlaryngectomy voice restoration are the electric artificial larynx, esophageal speech and prosthetic tracheoesophageal shunt speech.

Electric artificial larynx

The devices used for electric artificial laryngeal speech can be divided in mouth-types and transcervical types. The same principle of vibrations generated by an electromechanical mechanism is applied by both types of devices.

The oral device (e.g. Coopers-Rand Electric Speech Aid) introduces the battery powered sound through a small tube directly into the oral cavity. The articulatative structures of the vocal tract that are left over after a total laryngectomy, will modulate the sound to produce speech. The oral device can be applied immediately after surgery without causing pain or disturbing the recovery process.
The transcervical devices, e.g. Servox Inton, is placed against the neck to transmit the sound of the electromechanical source through the skin to the oral cavity. Voice generation occurs in the same way as with oral devices. The Servox Inton is a hand-held sound source which is rechargeable and has volume and pitch control settings. Drawback of the transcervical device is that proper placement against the neck can be difficult, especially when the neck is swollen or contains much scar tissue postoperatively. It is disadvantageous that using the electrolarynx one hand is required to speak, which also has a rather conspicuous appearance. An electrolarynx also produces a rather mechanical and monotonous speech.[42] This mechanical speech together with the hand-held system draws much attention to the disability. These disadvantages will limit the use of an electrolarynx.

Esophageal speech

Esophageal speech was introduced as the alaryngeal mode of speech when the air and food passages were completely separated by closing the troublesome pharyngostoma during total laryngectomy. To produce conventional esophageal speech air must be transported from the mouth into the esophagus. This air column is used as the energy source of esophageal voice production. The collected air is released upwards through the pharyngoesophageal segment (PE-segment), where the sound is produced. Intelligible speech can be achieved by modulating the esophageal sounds with the remaining structures of the vocal tract.[45] There are several different methods of air transport to the esophagus.[42,45] With the swallowing method air can be pushed into the esophagus by swallowing actions.[46,47] Another method is the inhalation method of esophageal speech. The patient creates a negative intrathoracic

pressure during inspiration. This negative pressure is transmitted to the esophagus. With relaxation of the PE-segment air will flow through the mouth passing the PE-segment into the esophagus until the air pressure differences are equalized.[48,49] In case of the injection method the patient moves the floor of the mouth to increase intraoral and pharyngeal pressure. Subsequently the PE-segment will open thus making air passage to the esophagus possible.[42,45] This can be done by using either the plosive injection method or the glossal press or tongue pomp injection method.[42,45-47] Although esophageal speech provides the laryngectomized patient with a low-pitched and low intensity speech,[49] a more natural voice quality can be achieved compared with the electrolarynx. Another advantage is that esophageal speech is hands-free. The main disadvantage is that only 25-50 % of laryngectomized patients will acquire functional esophageal speech.[50-52]

Prosthetic tracheoesophageal shunt speech

In 1979 Blom and Singer introduced the first commercially available tracheoesophageal shunt prosthesis.[44] This so-called "Duckbill" voice prosthesis was made of medical grade silicone rubber. The prosthesis was inserted in a surgically created fistula between the trachea and the esophagus by an endoscopic puncture technique. This technique was designed only for secondary placement some time after total laryngectomy. The valved prosthesis protected the laryngectomee against aspiration and at the same time prevented stenosis of the fistula. The prosthesis not only prevented aspiration but also allowed air passage from the trachea to the esophagus. By closing the tracheostoma pulmonary air can be directed from the trachea to the esophagus to pass the PE-segment where the basic sounds are produced (Fig. 2).
After the introduction of the "Duckbill" voice prosthesis many other silicone rubber prostheses have been developed. The first generation tracheoesophageal voice prostheses were determined to have a rather high resistance to airflow.[53-56] Later, low resistance valved voice prostheses became available, which further improved tracheoesophageal speech efficiency.[55-58] Basically the

Figure 2

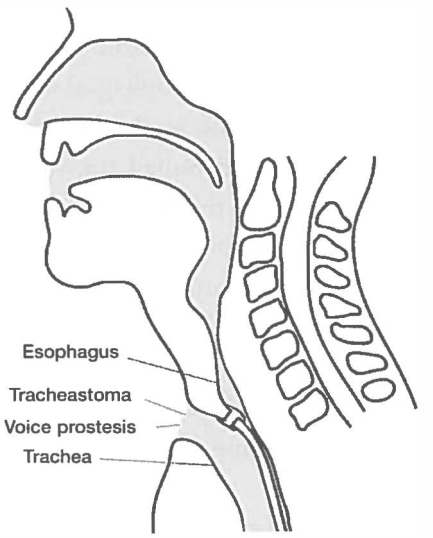

Figure 2. Schematic drawing of the situation after laryngectomy with a tracheo-esophageal voice prothesis placed in the tracheoesphageal fistula.

various voice prostheses can be divided into the non-indwelling voice prostheses (e.g. Blom-Singer and Bivona valves) and the indwelling voice prostheses (e.g. Groningen and Provox prostheses). The non-indwelling types are designed for secondary placement and can only be inserted after a patent tracheoesophageal fistula has been formed. The non-indwelling voice prostheses, which can be removed and replaced by the patient daily for cleansing, can lead to frequent displacements and fistula problems.[59] Development of the indwelling voice prostheses decreased prosthesis-related complications and improved patient comfort.[60] The indwelling biflanged prostheses have self-retaining capacities with respect to the tracheoesophageal fistula. They do not require daily maintenance, thus cannot be removed by the patient. These devices must be replaced by a physician or a skilled medical professional using specially manufactured instruments.[61,62] Replacement is generally a limited outpatient procedure under local anaesthesia of the oropharynx and trachea on request of the patient. However, regular replacements of the

prostheses may lead to incompetence of the tracheoesophageal fistula.[63] Scarring and fibrosis of the fistula can cause shunt insufficiency with external leakage of fluids. The insertion method of the first generation indwelling voice prostheses is basically a backloading system. A flexible guide wire is introduced through the tracheostoma and the tracheoesophageal fistula into the esophagus. Subsequently the wire is advanced up to the mouth. A new device is attached to the tip of the guide wire and pulled transorally into position after the dysfunctional prosthesis has been removed out of the fistula.[61,62] Sometimes the patient can experience gagging and coughing during this procedure, so it is still not considered as a comfortable and patient friendly replacement technique. Therefore new frontloading procedures have been introduced.[64-66] The main principle of the frontloading system is insertion and removal of the voice prosthesis via the tracheostoma. This method is judged to be less bo-thersome than the backloading system and it is consequently less inconve-nient for the patient.[67]

Tracheoesophageal shunt speech by using voice prostheses is generally considered to be superior to any other method of voice rehabilitation after total laryngectomy.[68,69] The major disadvantage of the silicone rubber voice prosthesis is their limited device life. For the indwelling voice prostheses an average *in situ* lifetime of 3-5 months is reported.[59,63,70] The device life is determined by the normal wear and tear of the silicon rubber, colonization and deterioration of the silicone surface by a covering biofilm of microorganisms (this will be discussed later on in this chapter). This can lead to irreversible damage to the silicone rubber and a dysfunctional valve with leakage of food and fluids, with or without an increased airflow resistance through the device.[71,72] Also other problems are encountered with prosthetic tracheoesophageal speech.[73,74] Beside leakage through a voice prosthesis, leakage around a prosthesis can occur. This occurs if a tracheoesophageal fistula is not viable due to repeated dilatation or fibrosis of local tissue will lead to failure of naturally tighten around the shaft of the prosthesis. This problem can be overcome by inserting a device with a larger outer diameter of the shaft and injection of collagen in the edges of the fistula to narrow the fistula. If these measures fail to solve the problem temporary removal of the prosthesis will spontaneously lead to shrinkage of the fistula, which after a regular pros-

thesis can be fitted. Surgical closure of the fistula with subsequent insertion of a new prosthesis as a secondary procedure can be necessary in difficult cases. Locoregional complications are: local inflammation and/or infection, migration of the fistula tract, dislocation of the prostheses, granulation tissue formation, fibrous tissue formation, hypertrophic scarring, esophageal stenosis or stricture, swallowing problems, tracheostomal stenosis, pulmonary aspiration, and pharyngeal constrictor spasm. Many of the mentioned problems can be managed by simple measures as antibiotic treatment, prosthetic replacement, or surgical revisions.

The Groningen Low Resistance, Groningen Ultra Low Resistance, Provox, Provox2, Blom-Singer indwelling low-pressure (Gelcap) and the VoiceMaser voice prostheses are well known commercially available low resistance indwelling voice prostheses in Europe and the United States (Fig. 3 a-f). Basically, these prostheses are manufactured from medical grade silicone rubber, which are produced in variable shaft lengths with flanges (appendix). The flanges at both ends provide retention of the device in the tracheoesophageal fistula, as well as some internal sealing against leakage of fluids around the prostheses. There are clear differences in valve design of these prostheses. The Groningen Low Resistance voice prosthesis has a semicircular slit of 145° in the hat of the esophageal flange. To reduce the transdevice air flow resistance the slit of the Groningen Ultra Low Resistance prosthesis was enlarged to 200°. The Provox, Provox 2 and the Blom-Singer Gelcap indwelling voice prostheses are all devices with an incorporated hinged valve. The preloaded hinged valve of both Provox prostheses close against a fluoroplastic ring at the esophageal flange. A different one-way valve design is used in the VoiceMaster prosthesis, in which a centered ball valve is incorporated in a star shaped esophageal flange. The silicone rubber ball valve retains against a titanium sleeve in closed position. The Groningen and the original Provox prostheses are inserted in the patient by using a backloading technique. On the other hand the Provox2, Blom-Singer indwelling low-pressure (Gelcap) and the VoiceMaster voice prostheses use an insertion method based on frontloading principles.

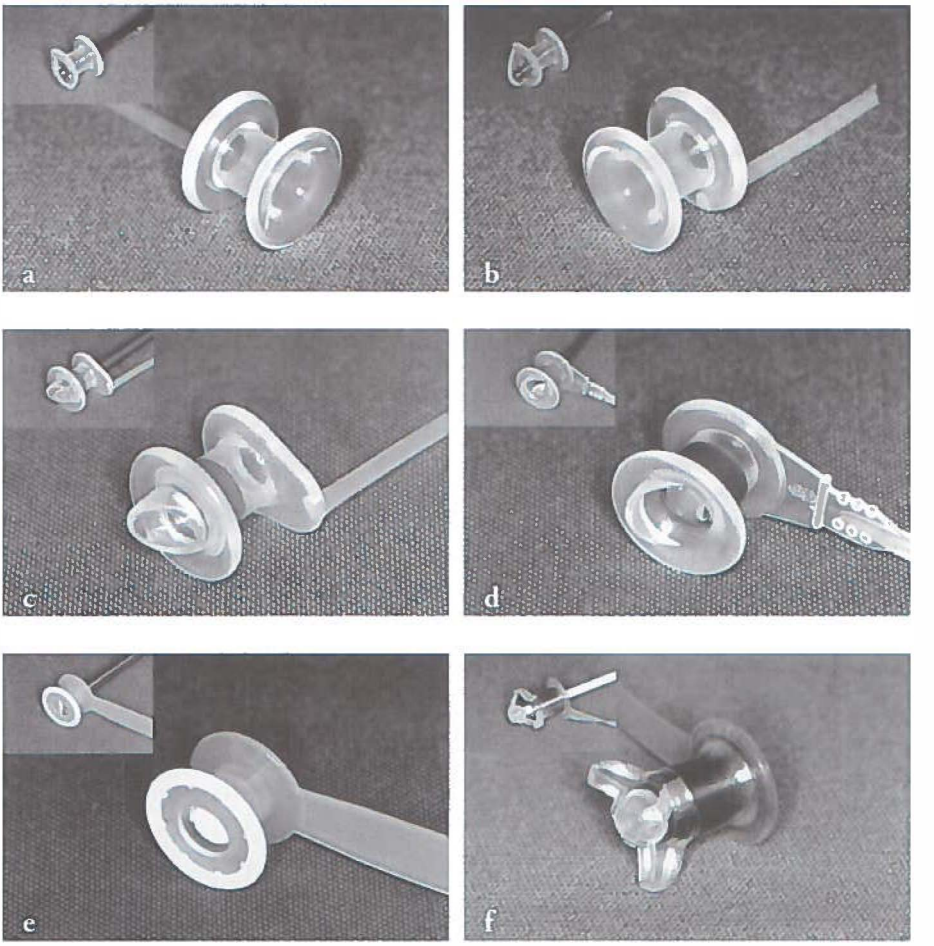

Figure 3. Six different indwelling voce prostheses, Groningen Low Restistance (a), Groningen Ultra Low Restistance (b), Provox (c), Provox2 (d), Blom-Singer indwelling low-pressure (Gelcap) (e) and the VoiceMaster prosthesis (f).

Biofilm formation on silicone rubber voice prostheses

Medical grade silicone rubber is a widely *in vivo* used biomaterial for example in intravascular, urinary and peritoneal dialysis catheters, mammary implants and testicular implants. Colonization of the surface of these biomedical devices with microorganisms has been well documented.[75-77] Studies of removed dysfunctional silicone rubber voice prostheses have shown that they gradually become colonized with microorganisms too. The esophageal flange of the voice prosthesis is located in a non-sterile area of the proximal esophagus. This is one of the reasons why this part of the voice prosthesis can be easily colonized by various microorganisms. Rapidly, a thick biofilm will form, particularly on the esophageal site and valve of the prosthesis. In the end this will interfere with the opening and closure of the one-way valve mechanism, which primarily prevents leakage of esophageal contents into the trachea. Also, the low-resistance features of the valve mechanism may be diminished by the biofilm formation. Microbial analysis of biofilms have shown that these biofilms consist of a mixed population including Candida Albicans and Candida tropicalis , oral streptococci and skin staphylococci.[77-83] In general Candida species seems to be responsible for the microbial overgrowth of voice prostheses, while bacteria are suggested to have another role. Leakage of fluids and food through the prosthesis is seen in relation with streptococci. Increased effort to speak due to increased transdevice airflow resistance is correlated with enterococci.[82] In other studies bacterial adhesion is suggested to be a precondition for effective yeast colonization on the surface of silicone rubber voice prostheses.[79,81,84] Previous studies aimed to prevent biofilm formation were conducted in clinical setting which often were based on a trial and error principle, the results of these attempts were varying. The results of oropharyngeal decontamination with amphotericin B lozenges was promising in reducing the Candida colonization on the prosthesis, but the findings were based upon only on ten patients.[85] Within the population under investigation therapy compliance was also difficult. To overcome this compliance problem application with a buccal bioadhesive slow-release tablet containing antimycotics have been suggested.[86] There was a distinct reduction of fungal colonization of the voice prostheses. The device life was unfortunately not

subject of investigation. However, antimicrobial resistance induced by long-term use of antimycotics is a potential risk of these therapies. Consensus about frequent cleansing of the prosthesis with or without the use of antimycotic agents have never been achieved. To come to less frequent prosthesis replacements more evidence based research on biofilm formation on silicone rubber voice prostheses has to be performed. Further understanding of the mechanism of biofilm formation is essential. In optimal environmental conditions (availability of nutrients, moisture and temperature) biofilm formation on silicone rubber voice prosthesis, just like other biomedical implants, is a matter of course. The first step in biofilm formation is the absorption of a conditioning biofilm, i.e. saliva in case of voice prostheses.[87,88] After this step transport and adhesion of the microorganisms followed with subsequent attachment, growth and eventually ingrowth in the silicone material.[89] Based on this theory further research has led to modifications of surface characteristics of silicone rubber voice prostheses without changing the mechanical properties of the silicone rubber material.[90] Although the results are promising there is a great demand for comprehensive clinical evaluation of these preliminary results.

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Chapter 3

THE *IN SITU* LIFE TIME OF THE GRONINGEN LOW RESISTANCE AND PROVOX2 TRACHEOESOPHAGEAL VOICE PROSTHESES

Leunisse C,Tjong Ayong HJ, Van Weissenbruch R, Albers FWJ. Device life of the Groningen Low Resistance and Provox2 tracheoesophageal voice prostheses. Submitted

Introduction

Total laryngectomy remains an important treatment modality in the cure of laryngeal and pharyngeal cancer, and occasionally in severe swallowing disturbances and aspiration. Although a total laryngectomy can be life saving, it has a great influence on patient's quality of life. The loss of speech has major psychological and social consequences for most laryngectomees[1]. Lately, voice rehabilitation has been subject of substantial experimental and clinical research, resulting in the tracheo-esophageal shunt speech as the current restoration modality of choice.

Since the introduction of the tracheoesophageal shunt prosthesis in 1979, several modified devices have been investigated internationally.[2] The original non-indwelling device must be removed by the patient for daily maintenance, while indwelling devices only need occasional changing. At first, these devices were inserted in patients by a backloading technique. Today changing the prosthesis is possible using a convenient frontloading principle. This insertion technique is much more comfortable, for patients as well as physicians. A major disadvantage of the silicone indwelling voice prosthesis is the limited *in situ* lifetime, due mainly to biofilm formation and deterioration of the silicone material of the prosthesis.[3]

The Department of Otorhinolaryngology of the University Hospital Groningen has a comprehensive experience in developing and applying tracheoesophageal shunt prostheses. From the early 1980's the Standard Groningen prosthesis, and subsequently the Groningen Low Resistance prosthesis has been used.[4,5] Both these devices are inserted on a backloading basis. After the development of the Provox2 voice prosthesis in 1996, this frontloading prosthesis was gradually introduced in the Groningen clinic.[6] The simultaneous use of various types of shunt prostheses revealed subjective differences in quality, such as a presumed shorter *in situ* lifetime of the Provox2 prosthesis. In this study a retrospective analysis was performed on 102 patients after total laryngectomy, with special emphasis on the survival time of the tracheoesophageal prostheses in relation to relevant variables.

Materials and methods

The medical files of 102 patients who underwent a total laryngectomy at our department between January 1993 and November 1999 were analysed. In our department the treatment of laryngeal cancer depends highly on the TNM classification. In small tumours (T1 and T2) the treatment of first choice is radiotherapy. Total laryngectomy mostly followed by postoperative radiotherapy is performed in T3 and T4 classified tumours and in cases of recurrence after initial radiotherapy. Lymph node metastasis is treated by an additional unilateral or bilateral neck dissection. Tracheoesophageal puncture and insertion of the first voice prosthesis together with pharyngoesophageal myotomy is performed in all patients at the time of operation. The first voice prosthesis is always a Groningen Low Resistance prosthesis. At the end of a device life, a voice prosthesis is replaced at the outpatientclinic.

Before 1996 all the patients were fitted with a Groningen Low Resistance prosthesis, because the Provox2 prosthesis was not yet available. This explains the fact that, of the 102 laryngectomy patients, some have used only a Groningen Low Resistance prosthesis while other have had both Groningen Low Resistance and Provox2 prosthesis inserted. It also accounts for the difference in replacement numbers between these two types of prosthesis.

From the total patient cohort, 24 died and in 16 of the cases the voice prosthesis was removed without insertion of a new prosthesis, followed by spontaneous or surgical closure of the tracheoesophageal fistula. All the accomplished voice prosthesis replacements in these patients were evaluated.

The following parameters from the medical files were obtained: age, sex, radiotherapy treatment, tumour site, TNM classification and valve insertion. From each valve insertion the interval of subsequent valve replacements, type of prosthesis and reason of replacement were recorded.

Mostly observed indications for replacement were salivary leakage through or around the valve prosthesis and inability to effectively produce voice due to increased airflow resistance of the prosthesis. Infrequently, valve replacement was indicated due to abundant granulation tissue formation and extrusion of the prosthesis.

Statistical processing was performed with computer-assisted program SPSS 8.0 for windows using the Mann-Whitney U-test and the Wilcoxon Signed Ranks tests. These two test were used because a symmetrical distribution of the data was not supposed. Survival type calculations were done by the product-limit method of Kaplan-Meier.

Results

Of the total group of 102 postlaryngectomy patients, 85 were men and 17 women. The overall mean age at laryngectomy was 62 years (range: 39-86 yrs). The mean age of male patients was 63 years and of female patients was 60 years. The follow-up since first insertion was 1-106 months (mean: 26 months, median: 17 months). The most common tumour site was the glottis (n=43, 42.2%) followed by supraglottis (n=39, 38.2%), hypopharynx (n=13, 12.7%), oropharynx (n=2, 2.0%) and transglottis (n=5, 4.9%). In 55.9 % of the cases, a laryngectomy was performed because of recurrence after radiotherapy. Of the population 36 patients (35.3%) had nodal metastasis at diagnosis. Only 5.9 % of the patients did not receive any radiotherapy; all others underwent curative radiotherapeutical treatment of 60-70 Gy during 6-7 weeks before or after the laryngectomy.
A total of 710 valve prostheses were inserted in these patients. Of these replacements 402 were Groningen Low Resistance, 12 original Provox and 296 Provox2 voice prostheses. The original Provox prosthesis were not taken into consideration due to the low number. The reasons for removal of a total number of 698 Groningen Low Resistance and the Provox2 prostheses are summarized in table 1.
The difference in replacement reasons between the two types of prosthesis was only significant for leakage through the prosthesis ($p < 0.01$) and increased effort to speak ($p < 0.05$). On patient level, an inventory was performed for the replacement indications to determine wether these were equally distributed among the population under investigation. Data analysis revealed an equal distribution of the replacement indications for both groups.

Table 1. Frequency table of reasons for replacements of Groningen Low Resistance (GLR) and Provox 2 voice prostheses

Prosthesis replacement indications	GLR n (%)	Provox 2 n (%)
Leakage through prosthesis*	276 (68.7)	227 (76.7)
Increased effort to speech*	64 (15.9)	31 (10.5)
Leakage around prosthesis	20 (5.0)	8 (2.7)
Granulation tissue formation	9 (2.2)	5 (1.7)
Dislocation of prosthesis	7 (1.7)	11 (3.7)
Other	26 (6.5)	14 (4.7)

The mean *in situ* duration of all the Groningen Low Resistance prostheses was 132 days; compared to the mean *in situ* duration of the Provox2 prostheses of 70 days, there was a statistical significant difference ($p < 0.01$). The Kaplan-Meier survival curves of both the Groningen Low Resistance and the Provox2 prostheses are shown in figure 1. The mean lifetime of the first voice prosthesis (which was, in fact, always a Groningen Low Resistance prosthesis) was 180 days, which was significant longer ($p < 0.01$) than the mean lifetime (117 days) of all the other Groningen Low Resistance prostheses. A statistically significant difference remained apparent when the mean *in situ* duration of the Provox2 was compared with the Groningen low Resistance prosthesis except the first prosthesis ($p < 0.01$).

A mean of 7 prostheses were changed in each patient (range: 1-29). The mean valve duration per patient was 132 days, with a minimum of 12 and a maximum of 551 days. The average lifetime of the first Groningen Low Resistance prosthesis per patient was 179 days. This was significant longer (136 days) compared to the Groningen Low Resistance prosthesis that was not the fist prosthesis ($p < 0.05$). The average lifetime of the Provox2 prosthesis per patient was 90 days. Compared to the mean lifetime of all the Groningen Low Resistance per patient (157 days), this was significant shorter ($p < 0.05$).

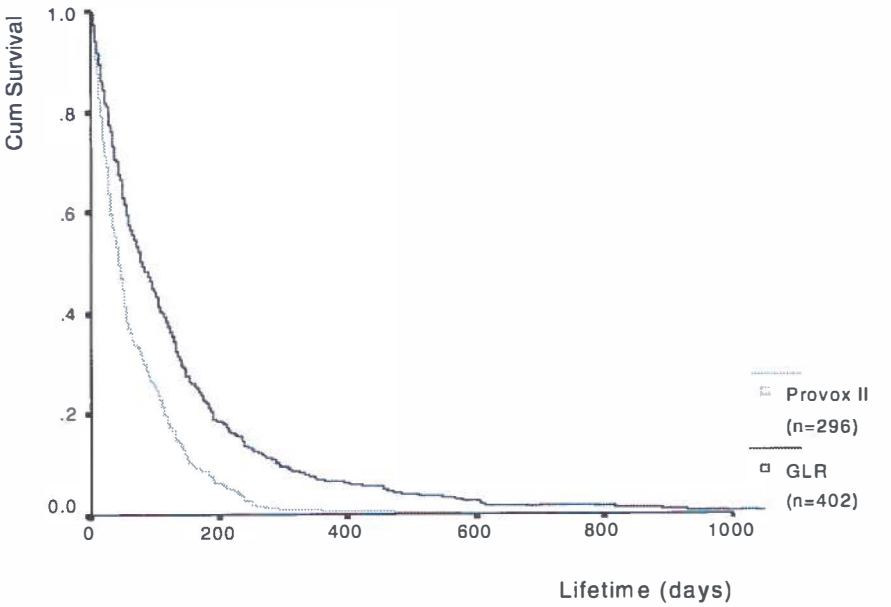

Figure 1. In situ lifetime of the Groningen Low Restistance (GLR) and Provox2 prosthesis (Kaplan-Meier plot). There is a significant different (p < 0,01)

There was no significant difference when compared to the Groningen Low Resistance that was not the first (p = 0.153).
Looking at the second through the tenth prosthesis replacements, the average lifetime of the Groningen Low Resistance prosthesis was (except for the eighth and the tenth) longer than the average lifetime of the Provox2 prosthesis. Only the third replacement showed a significant difference (p < 0.05). There was no significant difference (p = 0.9) of the mean *in situ life* time of a prosthesis for the prelaryngectomy radio-therapy group (n = 66) and the postlaryngectomy radiotherapy group (n = 30). Comparing the group of postlaryngectomy patients with (n = 30) and without postoperative (n = 72) radiotherapy, the postoperative radio-therapy group had a mean *in situ* lifetime of the first voice prosthesis of 145 days. For the non postoperative radiotherapy group this was 193 days. This difference was not significant (p = 0.10, fig. 2).

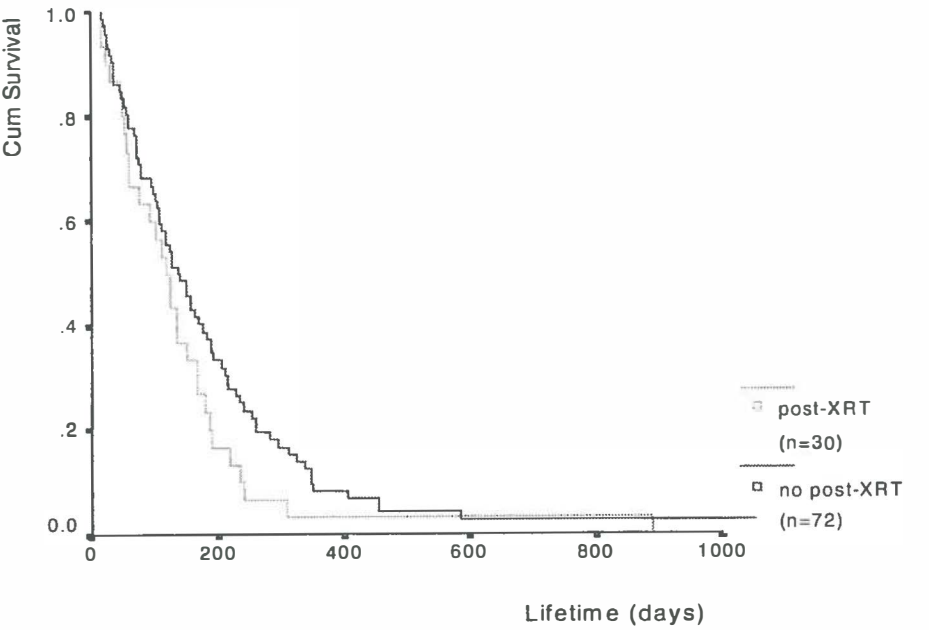

Figure 2. In situ lifetime of the first tracheoesophageal voice prostheses comparing the postlaryngectomy patients with and without postoperative radiotherapy (Kaplan-Meier plot). There is no significant difference (p = 0.10).

Discussion

The Provox2 prosthesis has distinct advantages for both patient and physician, due to the frontloading application. Nevertheless, evaluation of the *in situ* lifetime of the prosthesis is relevant because this prosthesis is significantly more expensive (almost twice cost-price) than the Groningen Low Resistance prosthesis. Although the mean *in situ* lifetime of the Provox2 prosthesis is shorter than that of the Groningen Low Resistance prosthesis, this difference appears not to be significant. Evaluation of the *in situ* lifetime of tracheoesophageal voice prostheses is possible in several ways. Considering all replacements in the whole study population, the difference of lifetime is significant. This significance disappears when the mean *in situ* lifetime of the

separate prostheses per patient is compared. This assumes that each individual prosthesis replacement can not be considered of equal statistical weight. There must be individual patient characteristics that influence the *in situ* lifetime of voice prostheses. Until now it has been difficult to identify these individual patient characteristics; the adverse influence of previous radiotherapy on the first voice prosthesis was the only reported factor.[7] Identification of specific patient characteristics would contribute to the development of specific interventions or even preventive measures to overcome rapid replacements.

The median lifetime of the Provox2 reported in literature was considerably longer. [8] In this study, only leakage through the prosthesis was taken into account as a reason for replacement. This could be a probable explanation for the longer median lifetime of the Provox2. The average *in situ* lifetime of the Groningen Low Resistance prosthesis as reported in literature was just shorter than in our study.[9,10] This comparison is difficult to interpret because in one of the studies in question, not only the Groningen Low Resistance but also the standard Groningen voice prosthesis[10] (and in the other study[9] only the standard Groningen voice prosthesis) was considered. The standard Groningen prosthesis had a higher transdevice airflow resistance compared to low resistance types of prostheses. It is not inconceivable that this prosthesis needed relatively rapid replacement, due to increased effort or even impairment to speak. Mahieu et al. described the shortest mean *in situ* life time without a clear specification of the replacement reasons. In another study, Van den Hoogen et al. did specify the reasons for replacements and described a rather high incidence of increased effort to speak, 45.4% in contrast with 15.9% in our study. The clinical impression exists that dislocation of the prosthesis, due to the specific frontloading insertion technique, occurs more often with the Provox 2 prosthesis. In this retrospective study we recognise that this complication is not well established; further understanding of this problem needs a prospective analysis.

At our Department all first valve prosthesis insertions were Groningen Low Resistance prostheses and all carried out as a primary procedure. This prosthesis was significantly longer *in situ* than any other subsequent prosthesis. This phenomenon can be partly explained by the fact that speech rehabilita-

tion and oral feeding start about two weeks postoperatively. In the acute postoperative period there is barely any mechanical load to this first tracheoesophageal shunt prosthesis. Further, adaptation of micro-organisms involved in biofilm formation could contribute to a much easier attachment to the silicone material. No influence was described on the survival of the first prostheses, if the prosthesis was *in situ* during radiotherapy.

In conclusion, the application of different types of tracheoesophageal shunt prostheses in a clinical setting needs to be evaluated over a longitudinal period of time. Such an evaluation should not only include aspects with regard to the speech quality, but also investigate the insertion method, *in situ* lifetime of the device , the reasons for replacements and the cost-effectiveness. With respect to quality of life, device life and replacement techniques should be considered when comparing voice prostheses and their respective influences on voice and speech rehabilitation.

The results of this study emphasize the importance of detailed analysis of the behaviour of tracheoesophageal shunt prostheses in relation to inter- and intraindividual variables.

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Chapter 4

AERODYNAMIC FEATURES OF SELF-RETAINING TRACHEOESOPHAGEAL VOICE PROSTHESES. STANDARDIZATION OF THE *IN VITRO* PROCEDURES

Leunisse C, Van Weissenbruch R, Wit HP, Albers FWJ.
Aerodynamic features of indwelling tracheoesophageal voice prostheses. Submitted

Introduction

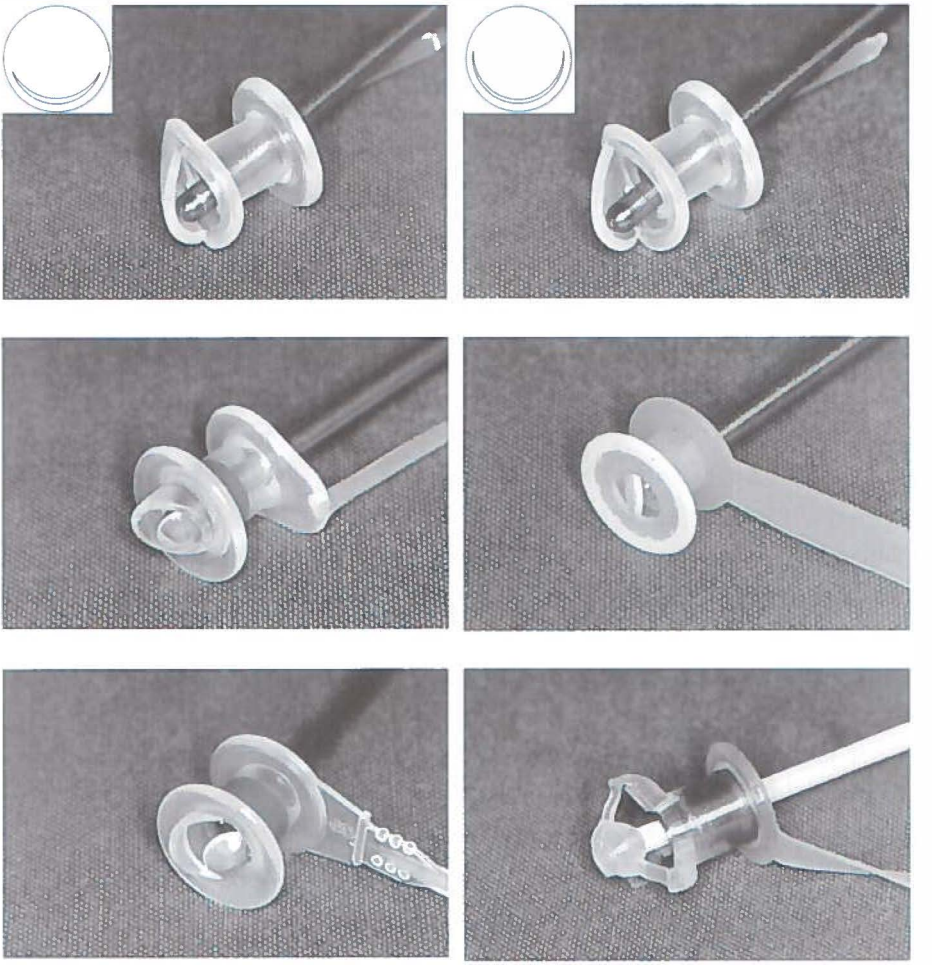
The most disabling consequence of a total laryngectomy procedure is the loss of normal laryngeal communication. Vocal functions can be successfully restored by using tracheoesophageal speech. Initially, the most important drawback of this shunt technique was aspiration through the tracheoesophageal fistula. In 1979 the use of tracheoesophageal shunt prostheses was popularized by Blom and Singer[1] and encouraged the development of various types of devices. These prostheses serve several functions. They permit shunting of exhaled air between the trachea and the esophagus, while the one-way valve prevents leakage of esophageal contents into the trachea.
Tracheoesophageal speech makes use of the natural air reservoir of the lungs. By occluding the tracheastome the intra-tracheal pressure is build up and expiratory air can be passed through the tracheoesophageal shunt prosthesis into the proximal esophagus. The basic sound source is located at the level of the pharyngoesophageal segment. The efficiency of this method of speech is also determined by known non-shunt prosthesis related factors such as the tonicity of the pharyngoesophageal segment and the patient's acuity[2]. However, the prosthesis predominantly determines the resistance to airflow thus speech efficiency. This resistance primarily depends on the design of the prosthesis especially the valve part of the prosthesis[3,4]. During usage the resistance will also be determined by the grade of contamination and deterioration of the voice prosthesis by oropharyngeal microorganism[5-7]. The first generation tracheoesophageal voice prostheses were determined to have rather high resistance to airflow[3,8,9]. Later, low-resistance valved prostheses were introduced[3,10,11],which further improved tracheoesophageal speech efficiency.
The non-indwelling prostheses, which can be inserted by the patient and requires daily removal by the patient for cleaning, can lead to frequent displacements and fistula problems[12]. Also, this technique is not suitable for every patient. Development of indwelling voice prostheses decreased prosthesis-related complications and improved patient comfort[13]. The indwelling prostheses have self-retaining capacities with respect to the tracheoesophageal fistula and do not require daily maintenance, thus cannot be removed by the patient. This device must be replaced by a physician using specially manufac-

tured instruments [9,14]. Although the replacement procedure can be done on an outpatient basis, it can still be considered as an inconvenient procedure for the patient. Regular replacements of the prostheses may also lead to incompetence of the tracheoesophageal fistula [15]. Scarring and fibrosis of the fistula may cause shunt insufficiency with external leakage of fluids. The insertion method of the first generation indwelling prostheses was basically a back loading system in which a guide wire was introduced to pull the prosthesis transorally into position. Because of the inconvenience of this procedure, new frontloading procedures have been introduced. The insertion of the voice prosthesis directly through the tracheostome into the fistula is the main principle of the frontloading system [16-18]. The latter method of insertion is judged to be performed more easily than the backloading systems and it is less uncomfortable for the patient.
This study was performed to evaluate the aerodynamic features of 6 different indwelling low resistance tracheoesophageal voice prostheses *in vitro* using a standardized setting mimicking the *in vivo* circumstances. All prostheses under investigation consist of all the latest design features including frontloading and/or backloading insertion techniques. The selected prostheses can be regarded as the most commonly used types in Europe and the United States at this moment.

Materials and methods

Types of prostheses

Figure 1 displays the 6 selected silicone rubber voice prostheses of which the aerodynamic properties have been examined. In table I some technical features of these prostheses are summarized. The Groningen Low Resistance voice prostheses has a semicircular slit of 145° in the hat of the esophageal flange. To reduce the transdevice air flow resistance the Groningen Ultra Low Resistance prosthesis with a slit of 200° was developed. The Provox, Provox 2 and the Blom-Singer Gelcap indwelling voice prostheses are all biflanged devices with an incorporated hinged valve. The design of the Voice



Figures 1. The six different low resistance tracheoesophageal voice prosthese, with opened valve, used in this study. Upper left the Groningen Low resistance, upper right the Groningen Ultra Low Resistance (in these pictures are inserted an overview of the slit valve design), middle left the Provox, middle right the Provox 2, bottom left the Blom-Singer Gelcap and bottom right the VoiceMaster voice prostheses.

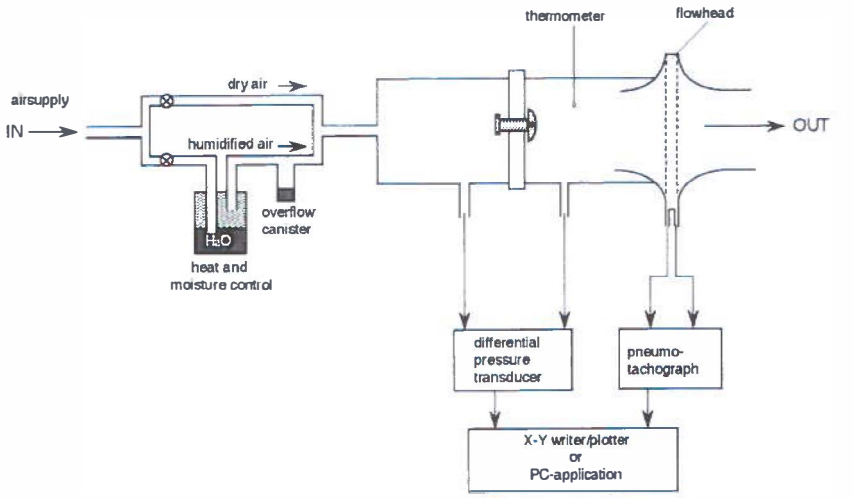
Table I. Characteristics of the silicone rubber tracheoesophageal voice prostheses examined in this study (LR = low resistance, ULR = ultra low resistance).

Prosthesis type	Insertion method	Valve type	Inner diameter	Manufacturer
Groningen LR	backloading	slit	4.9 mm	Medin (The Netherlands)
Groningen ULR	backloading	slit	4.9 mm	Medin (The Netherlands)
Provox	backloading	hinged	3.8 mm	Atos Medical AB (Sweden)
Provox 2	frontloading	hinged	3.9 mm	Atos Medical AB (Sweden)
VoiceMaster	frontloading	ball	4.9 mm	Entermed International (The Netherlands)
Blom-Singer	frontloading	hinged	3.8 mm	Inhealth Technologies (United States of America)

Master voice prosthesis consists of a silicone rubber ball valve attached to three silicone rubber branches. All the voice prostheses were obtained directly from the manufacturers. The prostheses were normal production devices already released for clinical application.

Measuring device

The experimental setup as shown schematically in figure 2 was used to perform the measurements. With this setup the transdevice air pressure loss (kPa) during a known transdevice airflow rate (l/s) of the device was repeatedly determined. The perspex tube consisted of three parts, which could be fitted into each other. The centre part consisted of a disc with a central hole. In this hole a custom made rubber ring was attached in which a specific voice prosthesis could be inserted, comparable to the *in vivo* situation. The perspex



Figures 2. Schematic representation of the experimental setup which was used for aerodynamic measurements.

test tube was separated by the prosthesis-holder in two separate chambers, one for the airflow inlet and the other for the outlet. Each chamber was connected to a differential pressure transducer (EMA 84; Erwin Halstrup Multur, Germany). With this pressure transducer the transdevice air pressure loss was measured. At the end of the tube, the outlet chamber was connected to a flow head (Mercury electronics, Glasgow Scotland). This flow head was attached to a pneumotograph (presograph-pneumotachygraph, Godart Statham) to record the transdevice air flow.
The pneumotograph was calibrated against a floating ball flow meter (Brooks, Sho-Rate). The signals from the manometer and the pneumotograph were transmitted to a x-y plotter (Hewlett Packard 7015B).

Measurements

Airflow used in this study ranged from 0.0-0.8 l/s. Of each type of prosthesis five devices were examined while three separate measurements were performed of each prosthesis. The median curve was selected and used for fur-

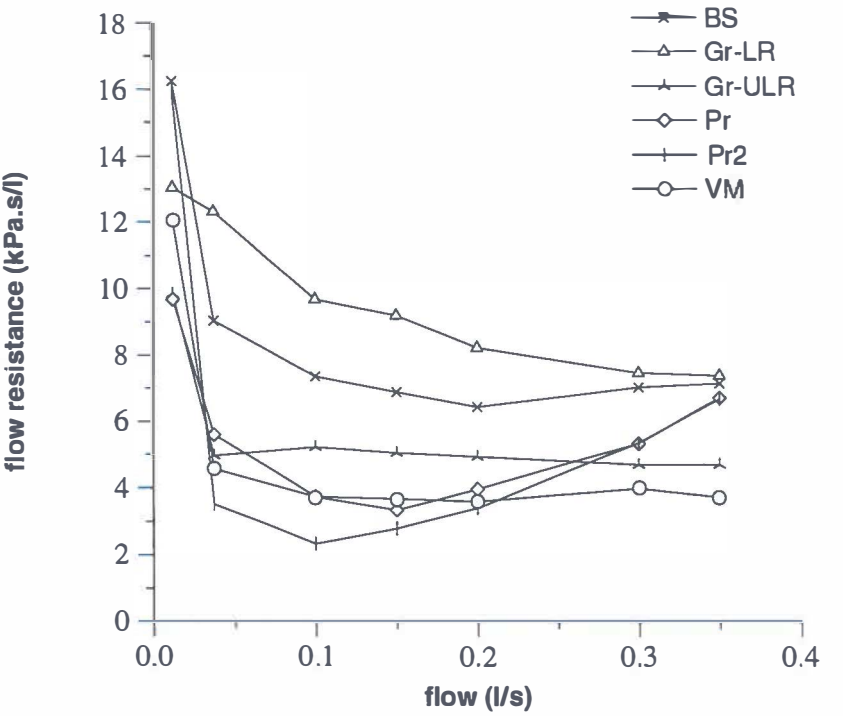
ther calculations. From this air pressure loss/ airflow curve transdevice resistance (kPa.s.l $^{-1}$) was derived by calculation of the slope of the air pressure loss/airflow curve at 0.0125, 0.0375, 0.10, 0.15, 0.20, 0.25,0.30 and 0.35 l/s, consecutively.
First, the measurements were performed with normal dry air at room temperature. In order to simulate the *in vivo* situation the measurements were also carried out with 100% humidified warm air. This was accomplished by passing the air supply through a reservoir with heated water (55 degrees Celsius). The 100% saturated warm airflow was controlled on the way to the plexiglass tube, while condensed water was drained in an overflow canister. At the time the air entered the flow chamber at the tracheoesophageal voice prosthesis the average temperature was decreased to 36 ° C. This was monitored by a continuous temperature registration.

Statistics

Statistical analysis was performed with computer assisted program SPSS 8.0 for Windows using the Mann-Whitney U-test and the Wilcoxon Signed Ranks test. These two test were used because a symmetrical distribution of the data was not supposed.

Results

In figure 3, the relation between the transdevice air resistance of the different prostheses and the airflow rate is shown. These results are obtained from the experiments with dry air. The selected data from the figure are summarized in table II.
The figure reveals that the transdevice air resistance of the Groningen Low Resistance and the Blom-Singer Gelcap prosthesis are considerably higher than the resistance measured of the Provox, Provox 2, Groningen Ultra Low Resistance and the VoiceMaster prothesis. At a flow of 0.15 l/s, which is considered to be the physiological airflow parameter in voice prostheses assisted speech [19], the mean transdevice air flow resistance of the Groningen Low



Figures 3. Airflow resistance for the six measured voice prostheses with dry air. The data points represent the mean airflow resistance values for 5 devices.

resistance, Groningen Ultra Low Resistance , Provox, Provox 2, Blom-Singer Gelcap and VoiceMaster voice prostheses are 9.2 kPa.s/l, 5.0 kPa.s/l, 3.3 kPa.s/l, 2.8 kPa.s/l, 6.8 kPa.s/l and 3.7 kPa.s/l, respectively.

At low airflow rates all the prostheses started with high transdevice air flow resistances, which gradually decreased with increasing air flow rates. In cases of the Provox, Provox 2 and the VoiceMaster prostheses, the transdevice airflow resistance decreased initially, but paradoxically increased with additional higher airflow rates. Moreover this tendency was less obvious for the VoiceMaster prostheses.

Table II. Mean resistance (kPa.s/l) and standard deviation (SD) of each type of voice prosthesis (n=5) at 7 air flow values measured with dry air. Each value representing the average of three resistance calculations for each of these 5 prostheses. BS= Blom-Singer Gelcap (indwelling low resistance) prosthesis, Gr-LR= Groningen Low Resistance prosthesis, Gr-ULR= Groningen Ultra Low Resistance prosthesis, Pr= Provox prosthesis, Pr2= Provox 2 prosthesis and VM= VoiceMaster prosthesis.

flow (l/s)	Gr-LR (n=5) mean±SD	Pr (n=5) mean±SD	Gr-ULR (n=5) mean±SD	Pr2 (n=5) mean±SD	VM (n=5) mean±SD	BS (n=5) mean±SD
0.0125	13.0±1.4	9.7±2.0	9.8±3.2	15.9±3.5	12.1±1.1	16.2±3.4
0.0375	12.3±4.7	5.6±1.1	5.0±0.4	3.5±1.8	4.6±0.2	9.0±1.6
0.10	9.7±2.4	3.7±0.3	5.2±0.4	2.3±0.5	3.7±0.6	7.4±0.9
0.15	9.2±2.1	3.3±0.5	5.0±0.3	2.8±0.2	3.7±0.6	6.8±0.8
0.20	8.2±1.8	4.0±0.6	4.9±0.4	3.4±0.2	3.6±0.4	6.4±0.9
0.30	7.5±1.7	5.3±1.2	4.7±0.3	5.3±0.3	4.0±0.8	7.0±0.5
0.35	7.4±1.9	6.7±1.3	4.7± 0.5	6.7±0.3	3.7±0.5	7.1±0.6

In figure 4 a comparison of the dry and the saturated warm air measurements of the different tracheoesophageal voice prostheses is given. At saturated warm conditions, the transdevice air flow resistance values appeared to be lower compared to the measurements with normal dry air.
Statistical analysis of the transdevice resistance values at flow 0.15 l/s of the different voice prostheses measured with dry air showed no significant differences between the Provox, Provox 2 and the VoiceMaster tracheoesophageal voice prostheses. For the Groningen Ultra Low Resistance there was no significant difference compared with the VoiceMaster voice prosthesis The p-values of this analysis are summarized in table III.

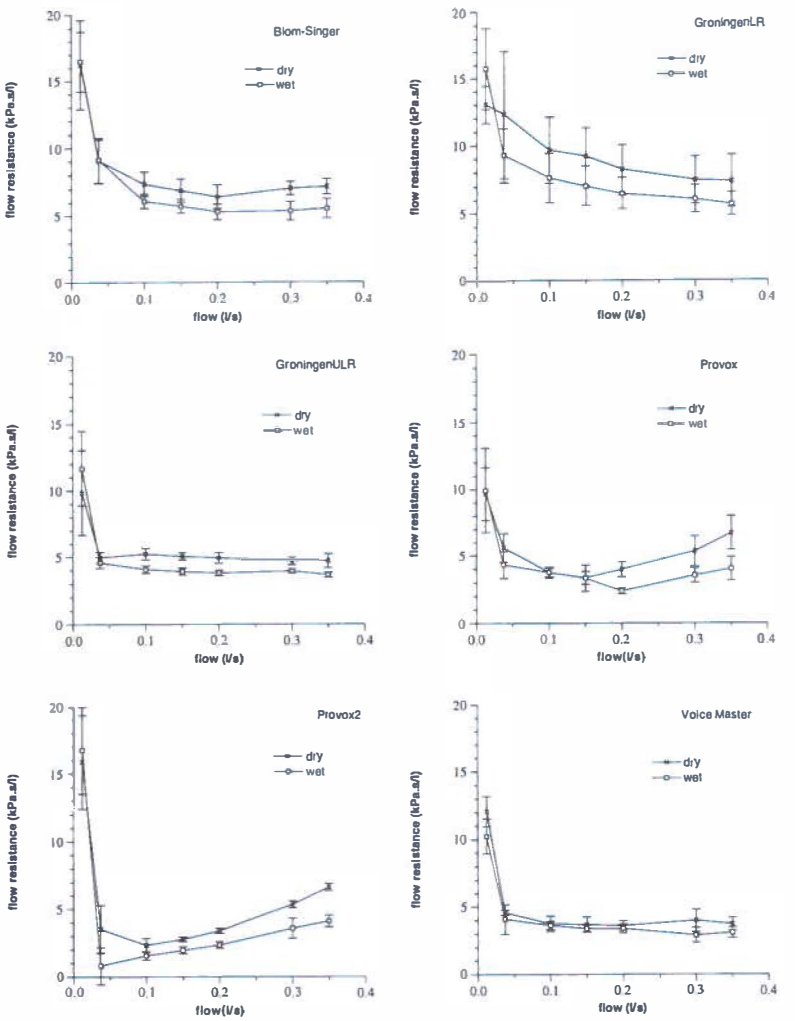


Figure 4. Airflow resistance and standard deviation of the dry and the warm humidified measurements in the different voice prostheses.

Table III. P-value which represents the statistical significance for airflow resistance at flow 0.15 l/s.

	Gr-LR	Pr	Gr-ULR	Pr2	VM
Pr	.009				
Gr-ULR	.009	.009			
Pr 2	.008	.072	.008		
VM	.009	.525	.016	.008	
BS	.117	.009	.009	.008	.009

In general the differences between the dry and saturated warm air measurements were significant at increasing flow rates. Only the VoiceMaster voice prosthesis showed no (significant) differences. An overview of the data is given in table IV.

Table IV. P-values representing the statistical significance for the transdevice airflow resistance difference between the dry and saturated warm air measurement. P-value <0.05 are printed in bold.

flow (l/s)	Gr-LR	Pr	Gr-ULR	Pr2	VM	BS
0.0125	0.225	1.000	0.042	0.357	0.068	1.000
0.0375	0.080	0.176	0.102	0.080	0.461	0.893
0.10	**0.043**	1.000	**0.042**	0.078	0.715	**0.043**
0.15	**0.043**	0.500	**0.043**	**0.042**	0.416	**0.042**
0.20	**0.042**	**0.043**	**0.043**	**0.042**	0.416	**0.043**
0.30	**0.042**	**0.043**	**0.042**	**0.041**	0.138	**0.042**
0.35	**0.043**	**0.043**	**0.043**	**0.043**	0.068	**0.043**

Discussion

The last 15 years voice rehabilitation after total laryngectomy with silicone rubber tracheoesophageal voice prostheses has undergone major changes. The introduction of low resistance prostheses has further facilitated tracheoeso-phageal speech. In this study the aerodynamic properties of 6 frequently used low resistance silicone rubber voice prostheses were determined. In contrast with previous studies, the transdevice airflow resistance was assessed in a different way.[3,10,11,20-22] In the past the transdevice airflow resistance was calculated from the ratio of the transdevice airflow pressure loss and the airflow. The relationship between the airflow pressure loss and the airflow is not linear, therefore it is physically incorrect to compute the transdevice airflow resistance from the ratio of the airflow pressure loss and the airflow. It is more appropriate to calculate the transdevice resistance by determining the slope of the airflow pressure/airflow curve at different flow values.

In our experiments the airflow resistance showed lower values using saturated warm air. For the majority of prostheses this was significantly different compared to the dry measurement. An explanation for this difference can be found in the fact that silicone rubber will get more soft and pliable at 36 degrees Celsius. This change in material condition can contribute to an easier opening of the silicone rubber valve of the prostheses. A liquid film on the silicone rubber material of the tracheoesophageal shunt prostheses may act as a kind of lubricant which also can facilitate the valve opening.

These results underline the importance of specific laboratory conditions which are necessary to simulate the *in vivo* situation as close as possible. In the literature the importance of the use of saturated warm air was denied.[11]

In order to compare results of other studies, a standardized experimental setup is necessary. In literature most studies are based on measurements performed with normal dry air under different laboratory conditions which will lead to inconclusive comparisons.

This study showed transdevice airflow resistance values of 7.04, 3.90 and 3.32 $kPa.s.l^{-1}$ at flow 0.15 l/s for the following voice prostheses: The Groningen Low Resistance, Groningen Ultra Low Resistance and Provox voice prostheses respectively. The results were obtained with the saturated warm measure-

ments. These values were lower compared to the reported results in literature. Previous research found transdevice resistance of 10.00 and 11.20 kPa.s.l^{-1} for the Groningen Low Resistance, 4.12 kPa.s.l^{-1} for the Groningen Ultra Low Resistance and 4.50 kPa.s.l^{-1} for the Provox voice prostheses. However, in one of this studies normal expiratory air was used while in the other two studies dry air at room temperature was applied. [3,11,23] Also the transdevice airflow resistance in these studies was calculated from the ratio of the transdevice air pressure loss and the air flow instead of determining the slope of the relation between these two parameters. In literature, no *in vitro* aerodynamic features are reported of the other examined voice prostheses.

Despite the fact that all studied voice prostheses are claimed to be of a low resistance type, there are still significant differences in transdevice airflow resistances. The Groningen Low Resistance and the Blom-Singer Gelcap indwelling low resistance prosthesis showed obviously higher airflow resistance, compared to the other devices. Reduction of airflow resistance have resulted in objective and subjective improvement of tracheoesophageal speech.[24,25] According to the laboratory results, the Provox, Provox 2, Gro-ningen Ultra Low Resistance, and the VoiceMaster prostheses seemed to be the preferred types. In general, the transdevice resistance is determined by the valve design and the diameter and the length of the tube part of the prosthesis.[4] The shaft contributes less to the transdevice airflow resistance when compared to the valve part. However, the contribution of the valve part decreases with increasing flow rate, while this is the opposite for the shaft. Although the Provox, Provox 2 and the Blom-Singer Gelcap indwelling low resistance prostheses are supplied with a comparable valve type, the Blom-Singer Gelcap has a significantly higher overall transdevice resistance. Since the inner diameter of these three devices is almost similar, the hinged valve of the Blom-Singer Gelcap prosthesis must be less efficient compared to both Provox types prostheses. The Provox 2 voice prostheses showed even slightly better airflow resistance figures than the original Provox prosthesis. An explanation for these differences can be based upon the following design changes considering the shaft of both Provox prostheses in which a fluoro plastic ring is embedded. The preloaded hinged valve of these prostheses closes against this fluoro plastic ring at the esophageal flange. The diameter of this ring (at valve side) of both pros-

theses is 3.7 mm according to the manufacturer. Accurate measurement of this diameter of 5 different prostheses of both types showed a inner diameter for the Provox and the Provox2 prostheses of 3.8 and 3.9 mm respectively. The influence of minimal diameter difference can be responsible for the aerodynamic differences between the two types of Provox voice prostheses. The importance of little diameter differences on the transdevice airflow resistance was already stressed in 1986.[26] The resistance rise at increasing flow rates of both types Provox prostheses is due to the narrower shaft dimensions at the esophageal side of the device. In comparison with the Provox and Provox 2 voice prostheses, the VoiceMaster prosthesis has a apparently larger inner diameter (4.9 mm). The VoiceMaster voice prostheses has also more favourable aerodynamic characteristics presumably due to the valve design and large inner diameter of the shaft. The transdevice airflow resistance is not decreasing with increasing flow rates. Both Groningen voice prostheses have identical inner diameters (4.9 mm), but significant difference in transdevice airflow resistance. The Groningen Low Resistance prosthesis has the highest resistance features despite a large inner diameter. This is most likely due to the valve mechanism. By enlarging the valve slit from 145 ^{0} to 200 ^{0} ,which has been done in the Groningen Ultra Low Resistance prosthesis, the resistance is reduced.

Satisfactory and efficient voice restoration with the Groningen Low Resistance, the Provox, the Provox 2 and the Blom-Singer Gelcap indwelling voice prosthesis have been reported.[17,24,27-29] Until now only few clinical reports have been published concerning the Groningen Ultra Low Resistance and the VoiceMaster voice prostheses. Only *in vitro* results of the Groningen Ultra Low Resistance prosthesis are available, while only preliminary data of the VoiceMaster voice prosthesis in a clinical setting have been published.[18,23] The mechanical and aerodynamic properties of voice prostheses can be successfully examined and compared in a laboratory setting. The current low resistance type tracheoesophageal voice prostheses provided with different valve designs show significant differences in transdevice airflow resistance. Although the devices with the lowest transdevice airflow resistance *in vitro* seem to be preferable, we have to keep in mind that the prosthesis with the lowest resistance in the laboratory might not be sufficient in patients. It is important to define how tracheoesophageal voice prostheses function *in vivo.*

Many other factors such as mechanical forces acting on the valves, deterioration of silicone rubber material, tonicity of the pharyngoesophageal segment, patients acuity, life time of the device, maintenance, and clinical experience with any specific prosthesis have to be taken in account when selecting an appropriate device.

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Chapter 5

THE ARTIFICIAL THROAT: A NEW METHOD FOR STANDARDIZATION OF IN VITRO EXPERIMENTS WITH TRACHEOESOPHAGEAL VOICE PROSTHESES

Leunisse C, Van Weissenbruch R, Busscher HJ , Van der Mei HC, Albers FWJ. The artificial throat: a new method for standardization of *in vitro* experiments with tracheo-esophageal voice prostheses. Acta Otolaryngol 1999; 119: 604-608.

Introduction

The loss of speech may be considered one of the most mutilating effects of total laryngectomy. Nowadays, tracheoesophageal voice prostheses have been used successfully for voice restoration after laryngectomy. Easy and quick rehabilitation of the laryngectomy patient is possible by shunting pulmonary air through the prosthesis situated in a tracheoesophageal fistula into the proximal esophagus. At the level of the pharyngoesophageal segment the basic sounds will be produced. Basically, the various voice prostheses can be divided into the non-indwelling voice prostheses (e.g. Blom-Singer /Bivona valves) and the indwelling voice prostheses (e.g. Groningen button and Provox voice prostheses). Primary as well as secondary insertions of indwelling prostheses are possible. The non-indwelling types can only be inserted after a patent fistula has been developed. The non-indwelling voice prostheses, which can be removed and replaced by the patient for cleansing, have a reported average device life of 2 months, but frequent displacements and fistula problems have been reported.[1,3] However, the indwelling voice prostheses have an average device life of 3-5 months .[2,3] The indwelling types have self-retaining capacities with respect to the tracheoesophageal fistula and cannot be removed for daily maintenance by the patient. These devices must be replaced by a physician using specially manufactured instruments. Although this procedure can be done under local anesthesia on an outpatient basis, it can still be considered an inconvenient procedure for the patient. Regular replacements of the prostheses may also lead to incompetence of the tracheoesophageal fistula.[4,5] Scarring and fibrosis of the fistula may cause shunt insufficiency with external leakage of fluids.

The esophageal flange of the voice prosthesis is located in a non-sterile area of the proximal esophagus. This is one of the reasons why this part of the voice prosthesis can be easily colonized by various microorganisms. Rapidly, a thick biofilm will form, particularly on the esophageal site and valve of the prosthesis. This will interfere with the opening and closing of the one-way valve mechanism, which primarily prevents leakage of esophageal contents into the trachea. Also, the low-resistance features of the valve mechanism may be diminished by the biofilm formation. The biofilm usually consists of a variety of

bacteria and yeasts. The biofilm may ultimately lead to irreversible damage to the silicone rubber and a dysfunctional valve with leakage of food and fluids, with or without an increased air flow resistance, through the device.[6,7] The majority of voice prostheses are made of silicone rubber and are more or less prone to this problem. The process of deterioration of the silicone rubber valve of the prostheses will ultimately limit device life.

Inhibition of biofilm formation can result in an increased device life with less frequent prosthesis replacements. Further research on biomaterials may reveal beneficial modifications to silicone rubber surfaces of voice prosthesis in relation to their specific environment. *In vivo* research of biofilm development is known to be difficult due to the heterogeneity of internal and external factors influencing the laryngectomy patient and the implant. Results of clinical trials are therefore difficult to compare and may lead to inconclusive results.

Another disadvantage of clinical research may be an ethical issue. Investigation of the process of biofilm development on the voice prosthesis in the patient will require removal of the prosthesis on a regular basis. This can be accomplished quite easily in the case of a non-indwelling prostheses. However, disruption of the biofilm during sampling may result in incomprehensible data. Removal of indwelling prostheses for research purposes will be more difficult or impossible to perform. Because clinical studies should be passed by local ethical committees, difficulty may be expected to get approval for such investigations. Assessment of device life will require a sufficient number of participants and will be very time consuming. This problem can be partially overcome by simulating the normal situation under laboratory conditions.

Assessment of colonization of biomaterials under laboratory conditions requires a method of developing biofilm *in vitro* which resembles the natural system. This comprehensive *in vitro* system must allow biofilm development, while also allowing simultaneous assessment of functional and morphological aspects. Based upon the concept of a 'Modified Robbins Device', *in vitro* colonization of complete voice prostheses was attempted after modification of the device.[8,9] The aim of this paper is to describe a system for *in vitro* simulation of oropharyngeal biofilm formation that can be used for all commer cially available types of voice prostheses.

Materials and methods

The artificial throat

The artificial throat consists of a flow-chamber made of Plexiglas. This material allows constant monitoring of the process of biofilm development (Fig. 1).[9]

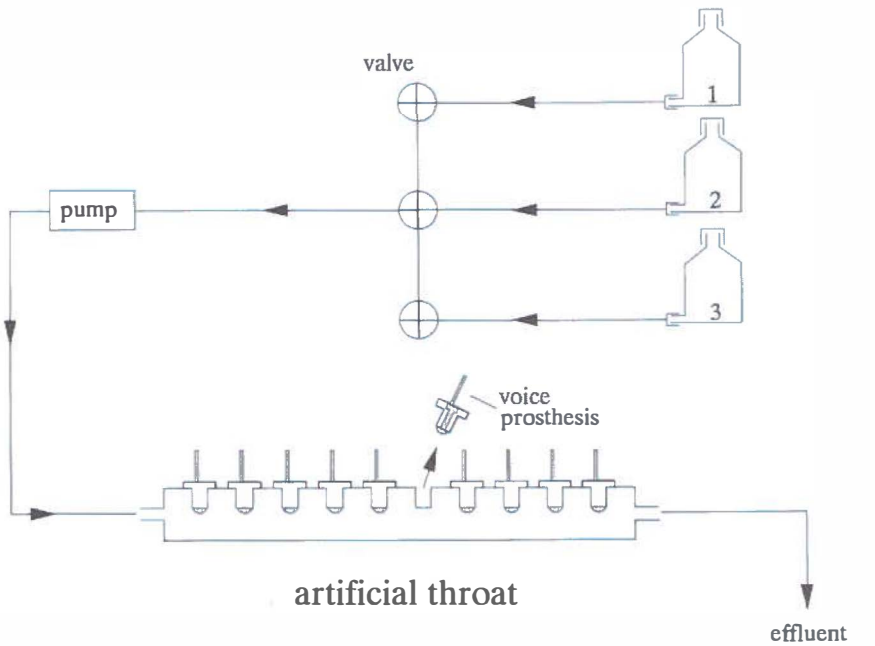

Figure 1. Schematic illustration of "the artifical throat". 1 = growth medium, 2 = phosphate buffer and 3 = test medium.

In the flow-chamber a number of sockets can be drilled on one side of the tube for insertion of plugs which hold the voice prostheses. We used a system with ten available positions in one flow-chamber. Every plug can be customized for insertion of any type or size of indwelling or non-indwelling voice prosthesis (Figs. 2 and 3).

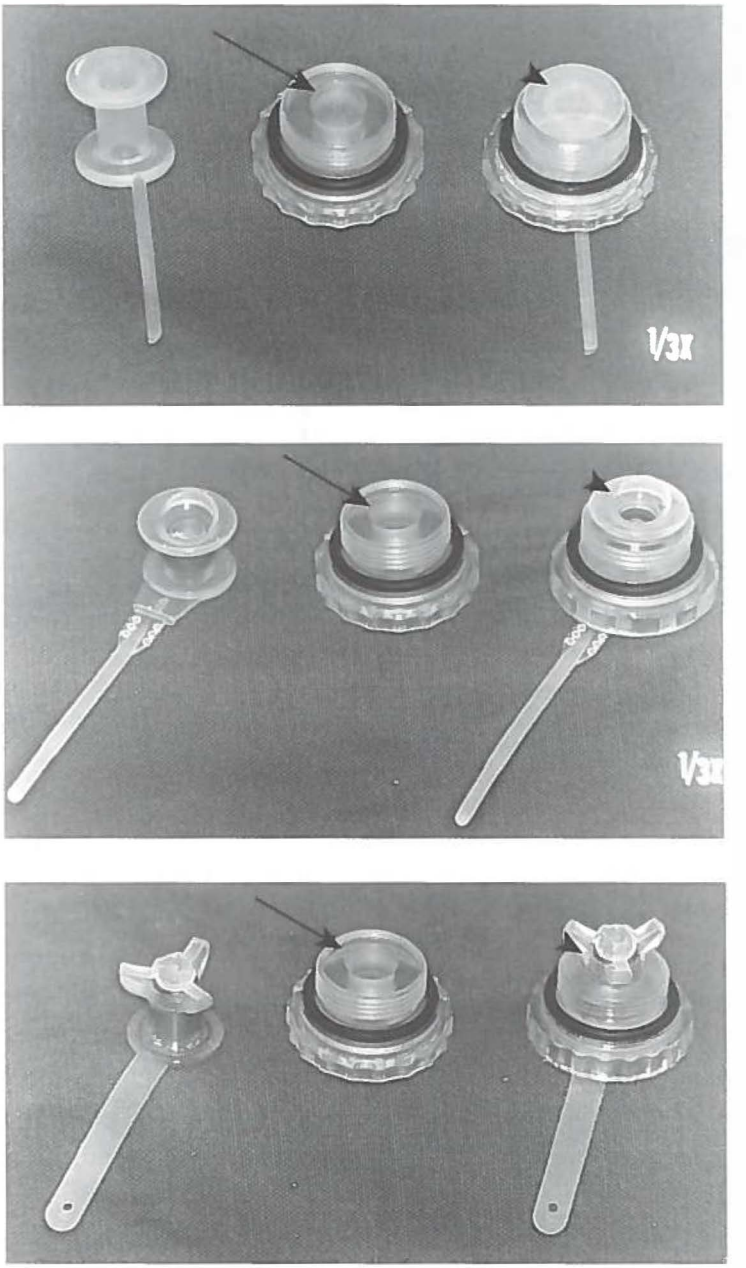

Figure 2. The Groningen button (a), the Provox2 (b), and the VoiceMaster (c) with a removable plug of "the artificial throat" (arrow) and the prostheses positioned in the plug (arrow head).

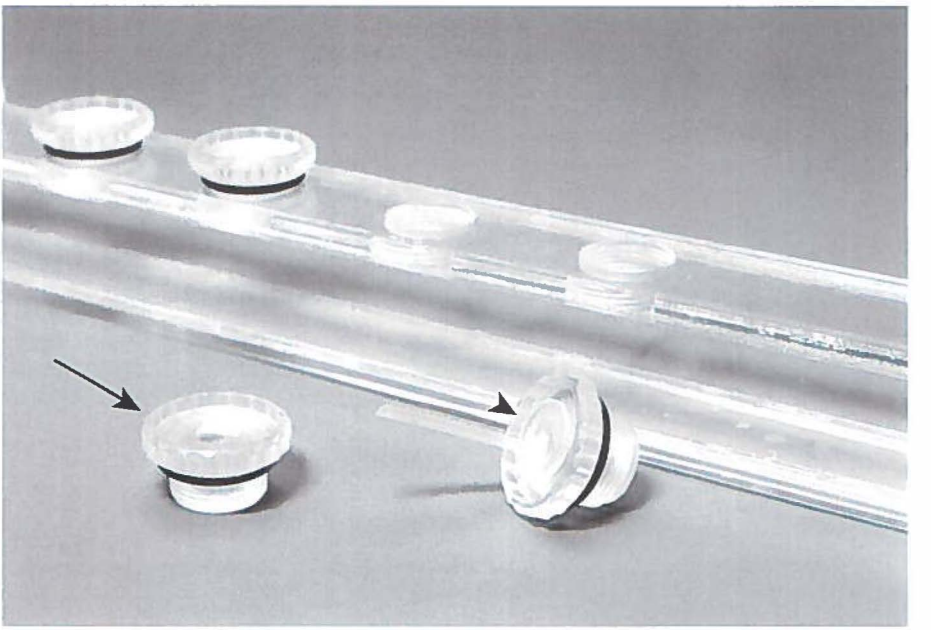

Figure 3, Removable plugs with (arrow) and withoput prosthesis (arrow head) in front of the Plexiglas transplant flow-chamber of "the artifical throat".

In the flow-chambers the esophageal (valve) part of the voice prosthesis is exposed to the culture of microorganisms, nutrient medium and buffer solutions. The valve side of the prosthesis is positioned in the lumen of the cubicle. In our initial experiments we only used the Groningen low-resistance button. This button is made of implant grade silicone rubber (Silastic Q 7-4750). The lumen of the shaft of the prosthesis has a diameter of 5 mm. As the length of the shaft does not interfere with the colonization of the esophageal flange, only one size (11 mm) of the Groningen voice prostheses was used. The plugs and prostheses can be removed from the artificial throat at any time for quantization or examination of the biofilm. Removal does not disturb the process of biofilm development or interfere with the attachment of the biofilm to the silicone rubber. After monitoring the development of biofilm on the esophageal surface, the voice prosthesis can be repositioned with the plug into the device. This will allow further longitudinal examination of biofilm development.

Several fluids and media can be passed through the device. Every flowchamber has input and output connectors on each side. During the experiments, the system is kept in a room with an average temperature of 23-25°C and atmospheric humidity of 100%.

Inoculation and sampling of the artificial throat

The artificial throat can be inoculated by single strain, or pure cultured microorganisms and biofilm mixture. The total cultivable micro flora derived from an explanted dysfunctional voice prosthesis was used to inoculate the artificial throat. This mixed culture contained various yeast and bacterial strains, such as *Candida albicans, Candida tropicalis, Streptococcus* and *Staphylococcus* species. After inoculation and sufficient sedimentation (3-4 hr) of the microorganisms on the voice prostheses, a 30% growth medium containing a mixture of 30% brain heart infusion (per liter 37 g BHI, OXOID, Basingstoke, Great Britain) and 70% defined yeast medium (per liter: 7.5 glucose, 3.5 g $(NH4)_2SO_4$, 1.5 g L-asparagine, 10 mg L-histidine, 20 mg DL-methionine, 20 mg DL-tryptophane, 1 g KH_2PO_4, 500 mg $MgSO_4.7H2O$, 500 mg NaCl, 500 mg $CaCl_2.2H_2O$, 100 mg yeast extract, 500 µg H_3BO_3, 400 µg $ZnSO_4.7H_2O$, 120 µg $Fe(III)Cl_3$, 200 µg $Na_2MoO_4.2H_2O$, 100µg KI, 40 µg $CuSO_4.5H_2O$, Merck, Darmstadt, Germany) was added to the system. Subsequently, a biofilm was allowed to grow on the voice prostheses over 3 days. On day 4 the device was perfused with phosphate buffered saline, pH 7.0, after which the prostheses were left in the moist environment of the drained device. During a period of 12 days the perfusion scheme was repeated 3 times a day. At the end of the day the artificial throat was filled with growth medium for 30 minutes and left to drain overnight.
On day 6, samples were taken from the deposits on the valve side of the prostheses. These samples were suspended in 1 ml of phosphate buffered saline (10 mM potassium phosphate pH 7.0 and 8.79 g/l NaCl), whereupon the suspension was oscillated for a period of 60 seconds (Ultrasonic vibrator, Transsonic TP690, CLMA). After serial dilution the samples were cultured on blood agar plates (general cultures) and BHI-agar plates (yeast cultures). After 3 days the colony forming units on the plates were counted (Colony

Counter, New Brunswick Scientific, Edison, N.J., U.S.A.) and the microorganisms were identified.

Monitoring of biofilm formation

After incubation the process of biofilm formation could be monitored through the transparent Plexiglas walls of the device. Over the following consecutive days the prostheses could be randomly removed for examination of the deposits, sampling and assessment of ingrowth of filamentous growing yeasts into the silicone rubber.
Scanning electron microscopy was used to evaluate biofilm formation and deterioration of the silicone rubber surface of the voice prosthesis. On day 12 the voice prostheses were removed from the insertion plug. After removal they were flushed twice (sucrose 6.8% in 0.1 M cacodylaat buffer pH 6.8) for a period of 30 seconds. Afterwards the prostheses were pre-fixated in a solution of glutaraldehyde 2% and 0.1 M cacodylate buffer. Post-fixation was performed by using a reduced TAO (tannic acid-arginine-OsO_4, Osmium) procedure. After fixation the specimens were step dehydrated twice (30-50-70-80-90-100% ethanol) for 1 hour and critical point dried with CO_2. This procedure was followed by coating the material with a thin layer of Gold(5 nm) (Ion Beam Sputter, Oxford Cryo). Scanning electron microscopy (SM-6301F, JEOL) was performed with different working distances and angles at 2 kV.

Results

After inoculation of the artificial throat successful development of biofilm on the esophageal flange of the Groningen voice prostheses was observed. During monitoring , a gradual increase of the deposits was noticed from day 1. By varying the supply of nutrients and buffer solutions, a representative biofilm was obtained, which covered the whole surface of the esophageal flange by day 12 (Fig. 4).

These deposits were solidly adhered to the material and could not be flushed away. During perfusion of the flow-chambers, spontaneous leakage of fluids through the prostheses was also observed. This seemed to be dependent on the amount of accumulation of the deposits on both the valve and the semi-circular valve-seating.

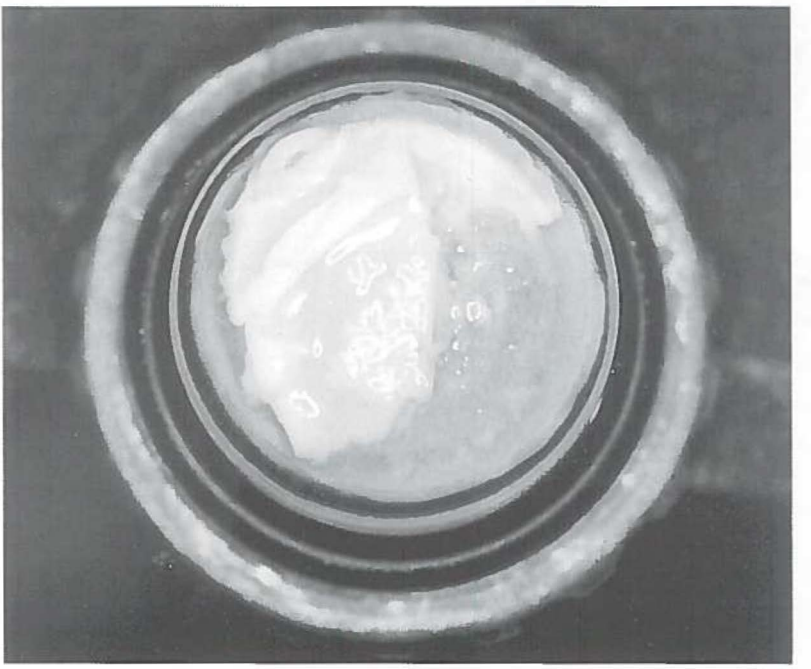

Figure 4. A plug containing a voice prosthesis with a biofilm covering the whole surface of the esophageal flange (day 12 of experiment).

Macroscopically, the deposits on the esophageal flange were similar to those seen on dysfunctional prostheses in patients. Scanning electron microscopy revealed the adhesion and attachment of the biofilm to the polymer surfaces. A comparable growth and ingrowth of microbes in the silicone rubber was present from the 4th day after inoculation (Fig. 5).

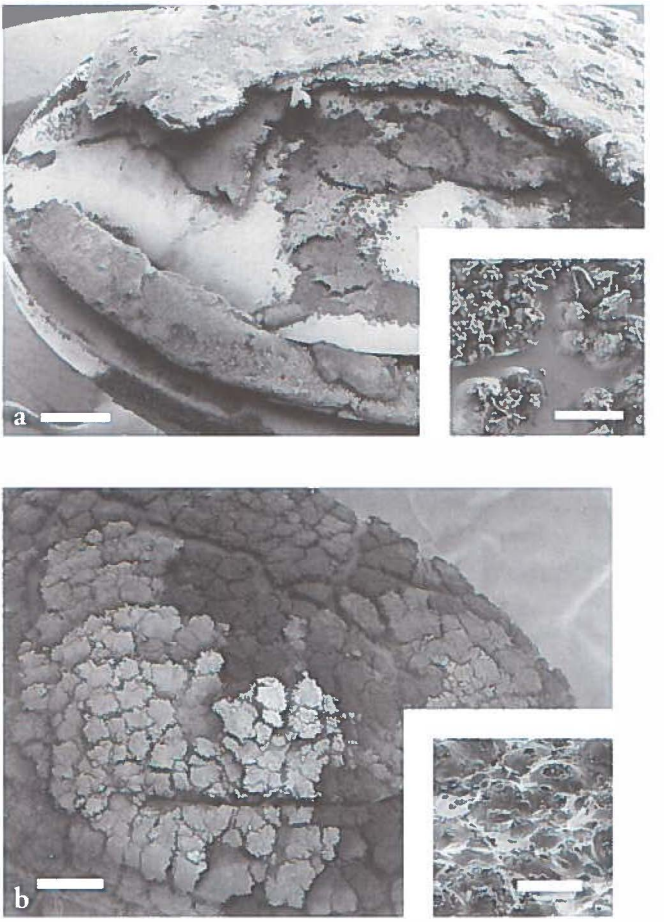

Figure 5. Scanning electron microscopy of the biofilm on a Grongen buttun (a) from " The Artificial throat" day 12 of experiment) compared to a biofilm of an explanted voice prosthese with a device life of 4 months (below). The bar equals 1 mm for the low magnification micrograph and 10 µm for the insert. On day 6 samples were taken from the biofilm. The cultures showed a mixed microflora of yeast and bacteria. The colony forming units (CFU) of bateria and yeats on blood agar plates and BHI-agar plates were 275 x 106/ml and 27 x 106/ml, respectively.

Discussion

In this study an artificial throat is introduced which allows biofilm formation on indwelling silicone rubber voice prostheses. These *in vitro* developed biofilm is highly comparable to the biofilm obtained from dysfunctional prostheses *in vivo*.[7,10,11] Studies in which microorganisms from explanted voice prostheses were analyzed demonstrated the typical heterogeneity of these microflora. However, these studies were not conducted in the same manner, and the results were neither reproducible nor comparable. We were able to create a biofilm which qualitatively bore a close resemblance to the *in vivo* situation. The deposits were macroscopically evident and were firmly attached to the silicone surface. Because ingrowth had already occurred, the deposits were difficult to remove.[11] The modified Robbins device has already been successfully used to observe the ingrowth phenomena of yeasts on silicone discs.[9,12] However, a more advanced state of the process of colonization was only observed by using the total cultivable cultures of removed dysfunctional voice prostheses. This observation may further confirm the importance of associative growths of yeasts and bacteria on the deterioration of silicone rubber voice prostheses *in vivo*.[10]

Scanning electron microscopy showed the colonization as well as the deterioration of the silicone material. Destruction of the silicone rubber surfaces was observed along with the filamentous growing yeasts surrounded by other microbes. In addition, the number of bacteria exceeded the total colony forming units of grown yeasts. This observation has also been reported in studies with explanted voice prostheses.[13,14]

The concept of the removable plug system allows longitudinal observation of the process of colonization without disrupting the biofilm formation. This interchangeable system not only allows temporary observation of the deposits, but also morphologic and functional studies of the deterioration of the silicone rubber. At the same time, several parallel devices can be applied for simultaneous observations on alternative processes or interactions. Also, the mechanical features of the one-way valve mechanism can be studied in more detail in association with the process of biofilm formation.

Finally, we conclude that the artificial throat is a promising system for further *in vitro* research of silicone rubber voice prostheses. Although the system can be modified to simulate numerous *in vivo* conditions, it cannot be considered an absolute substitute for clinical studies. In the patient numerous internal and external factors may constantly influence the colonization and dysfunction of silicone rubber voice prostheses. However, device life is primarily dependent on the biofilm. This makes the artificial throat extremely useful because it allows us to study the effects of single factors on the colonization process. These laboratory studies precede more comprehensive clinical trials.

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Chapter 6

BIOFILM FORMATION AND DESIGN FEATURES OF INDWELLING SILICONE RUBBER TRACHEO-ESOPHAGEAL VOICE PROSTHESES

Leunisse C, Van Weissenbruch R, Busscher HJ, Van der Mei HC, Dijk F, Albers FWJ. Biofilm formation and design features of indwelling silicone rubber tracheoesophageal voice prostheses. Submitted

Introduction

Voice is one of the basic human attributes. Therefore it is not surprising that the loss of voice may be considered as one of the most mutilating effects of total laryngectomy. Surgical removal of the larynx as primary treatment for laryngopharyngeal malignancies or as salvage treatment after recurrent cancer, will not only seriously effect the major laryngeal functions (phonation, airway control, swallowing, effort closure during strenuous activity and coughing), but will lead to disfigurement and uncertainty about the prognosis. Several methods for restoration of speech and voice have been attempted with various success rates. In 1979, the method of tracheoesophageal puncture and one-way valved voice prostheses was introduced which allowed easy and rapid establishment of functional tracheoesophageal speech.[1] In this technique pulmonary air is directed through a surgically created tracheoesophageal fistula to the cervical esophagus and pharynx. At the level of the pharyngoesophageal segment the basic sounds will be excited at the approximated surfaces.

The promising results of prosthetic voice restoration have led to the development of various types of prosthetic devices which, basically, can be divided into the indwelling types (e.g. Groningen button, Provox prosthesis) and the non-indwelling types (e.g. Blom-Singer, Bivona valves). The indwelling types or self-retaining prostheses can be inserted immediately after primary puncture at the time of laryngectomy or later as a secondary puncture, while the non-indwelling types can only be safely inserted as soon as a patent fistula has been developed.[2]

Since the esophageal part of the voice prostheses in patients have to withstand continuous mechanical, chemical and microbial influences in the cervical esophagus the one-way valve function will gradually diminish and give rise to increased phonatory efforts and leakage of esophageal contents into the trachea.[3] In case of valve failure the non-indwelling voice prostheses can be removed and replaced by the patient for cleansing, but frequent displacements and fistula problems have been reported.[3-6] The indwelling voice prostheses are practically maintenance-free, but daily cleansing with specially manufactured brushes or cotton swabs are advised. The indwelling types have self-retaining capacities with respect to the tracheoesophageal fistula and cannot be removed for daily maintenance by the patient. Replacements can be performed by simple anterograde or retrograde routes, but should be per-

formed by a trained medical professional in a clinical or outpatient setting.
The device life of voice prostheses can be determined by typical patient-related and prosthesis-related factors. The normal wear and tear of the voice prostheses depends on the intensity of daily use and cleansing, while the ingestion of various foods and fluids and the oropharyngeal flora will give rise to a polymicrobial colonization and deterioration of the valved prostheses.[4,7,8] The mean device life of the non-indwelling voice prostheses is reported to be approximately 2 months, while the currently used indwelling prostheses will function properly during 3-6 months.[4,9-11]
Inhibition of biofilm formation can result in an increased device life with less frequent prosthesis replacements. Further research on biomaterials may reveal beneficial modifications to silicone rubber surfaces of voice prosthesis in relation to their specific environment. *In vivo* research of biofilm development is known to be difficult due to the heterogeneity of internal and external factors influencing the postlaryngectomy patient and the implant. Assessment of colonization of biomaterials under laboratory conditions can now be performed by using special methods for growing biofilms *in vitro* which resemble the ecosystem in the patients' pharyngoesophageal segment. In a modified Robbins device, the artificial throat[12], prosthetic biofilm development can be initiated, while simultaneous assessment of functional and morphological aspects is allowed. This technique allows examination of the esophageal flange with the incorporated valve system in various prostheses. The aim of this paper is to describe biofilm formation on critical design features of the current most used voice prostheses in the artificial throat. These data may help to facilitate the development of more efficient valve designs and resistant biomaterials for these purposes.

Materials and methods

Voice prostheses

For this study we have selected four internationally used indwelling type silicone rubber voice prostheses which are applicable in almost all laryngectomees. In table I the specific valve designs and design features are specified.

Table I Overview of the specific valve designs and features of the selected voice prostheses.

Prosthesis type	**Manufacturer**	**Valve design**	**Materials** Tracheal flange	**Materials** valve	**Materials** valve seating
Groningen low resistance	Medin Groningen, The Netherlands	Semicircular slit valve	Silicone rubber	Silicone rubber	Silicone rubber
Provox2	Atos Medical Hörby, Sweden	Recessed hinged valve	Silicone rubber	Silicone rubber	radiopaque plastic ring
VoiceMaster	Entermed Instruments Woerden, The Netherlands	tripod ball valve	Silicone rubber	Silicone rubber	titanium sleeve
Blom Singer indwelling	Inhealth Technologies Carpinteria, CA, USA	recessed hinged valve	Silicone rubber	Silicone rubber	Silicone rubber

The selected voice prostheses as illustrated in figure 1, are each provided with a specifically designed one-way valve mechanism with optimal aerodynamic properties. Clinical experience over several years allowed us to define their mean device life and reasons for valve replacement.

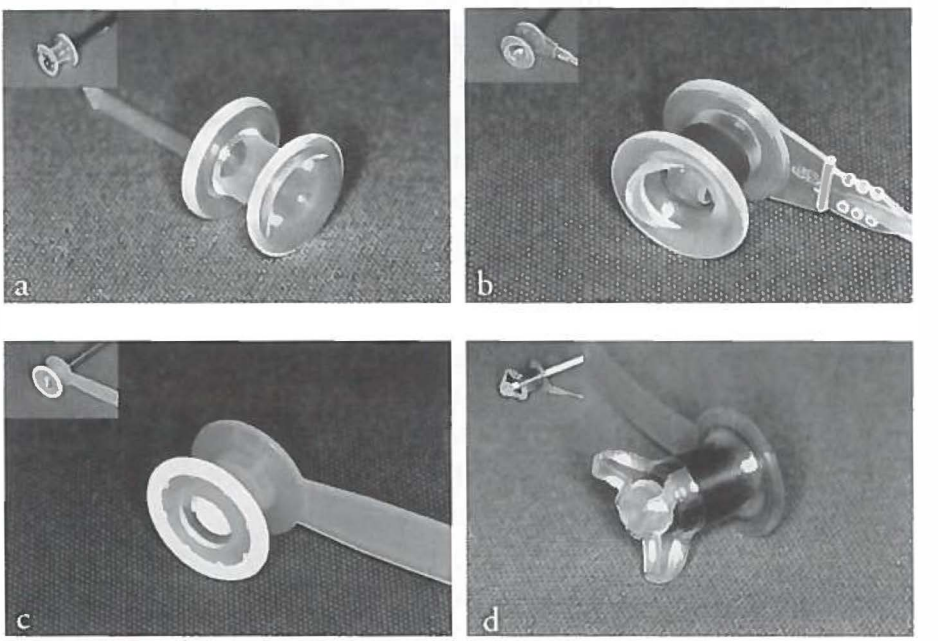

Figure 1. Illustrations of the Groningen low-resistance prosthesis (a), provox2 (prosthesis (b), Blom-Singer indwelling prosthesis (c) and VoiceMaster prosthesis (d). Each illustration is provided with an insert of the valve part.

Basically, the examined prostheses are manufactured from implant grade silicone rubber. The flanges at both ends provide retention of the device in the fistula, as well as some internal sealing against leakage of fluids around the prostheses. The current design of the majority of these prostheses is the result of several modifications to improve insertion, retention and aerodynamics. The traditionally Blom-Singer duckbill prosthesis equipped with a slit valve was replaced by a low-profile hinged valve design, which decreased airflow resistance. Both the Blom-Singer indwelling type and Provox2 voice prosthe-

ses make use of a hinged flap valve design that is incorporated in the esophageal flange[11,13], while the Groningen low resistance prosthesis is still successfully provided with a slit valved concept which has been often modified by increasing the slit valve angle.[14] A different one-way valve design is used in the VoiceMaster prostheses in which a centered ball valve is incorporated in a star shaped esophageal flange.[15] Most designs consist of a complete silicone rubber frame work. Only the VoiceMaster prostheses offer the silicone rubber ball valve which retains against a titanium sleeve in closed position. The susceptibility of various design features for biofilm formation can be studied under standardized laboratory conditions.

The artificial throat

The artificial throat consists of flow-chambers made of Plexiglas, which allows constant monitoring of the process of biofilm development (Fig.2).[12]
Each flow-chamber can be provided by a number of sockets on one side of the tube for insertion of plugs which can be customized for insertion of almost every available voice prosthesis. From each type of voice prosthesis 3 devices were randomly positioned in a flow-chamber. The valve side of the prosthesis, positioned in the lumen of the cubicle, is exposed to the culture of microorganisms, nutrient medium and buffer solutions. The plugs and prostheses can be removed from the artificial throat at any time for inspection of the biofilm. During the experiments, the system is kept in a room with an average temperature of 23-25°C and atmospheric humidity of 100%.

Inoculation and sampling of the artificial throat

The total cultivable microflora derived from an explanted dysfunctional voice prostheses was used to inoculate the artificial throat. This mixed culture contained various yeast and bacterial strains, such as *Candida albicans*, *Candida tropicalis*, *Streptococcus* and *Staphylococcus* species. After inoculation and sufficient sedimentation (3-4 hr) of the microorganisms on the voice prostheses, a 30% growth medium containing a mixture of 30% brain heart infusion (per liter 37 g BHI, OXOID, Basingstoke, Great Britain) and 70% defined yeast

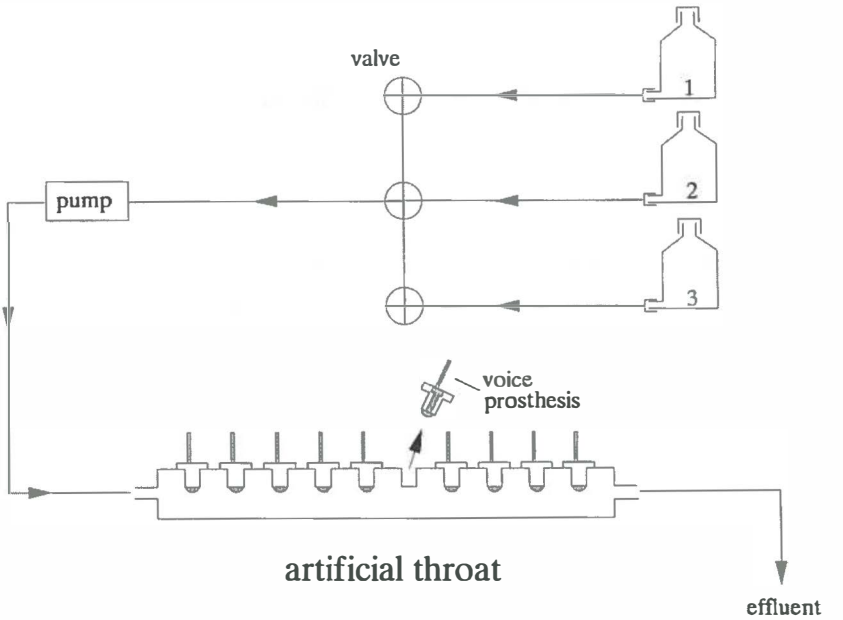

Figure 2. A schematic illustration of the artificial throat used for the biofilm formation on the several prostheses. Via the vials 1-3 the buffer solutions, biofilm cultures, and other suspensions can be supplied.

medium (per liter: 7.5 glucose, 3.5 g $(NH4)_2SO_4$, 1.5 g L-asparagine, 10 mg L-histidine, 20 mg DL-methionine, 20 mg DL-tryptophane, 1 g KH_2PO_4, 500 mg $MgSO_4.7H2O$, 500 mg NaCl, 500 mg $CaCl_2.2H_2O$, 100 mg yeast extract, 500 µg H_3BO_3, 400 µg $ZnSO_4.7H_2O$, 120 µg $Fe(III)Cl_3$, 200 µg $Na_2MoO_4.2H_2O$, 100µg KI, 40 µg $CuSO_4.5H_2O$, Merck, Darmstadt, Germany) was added to the system. Subsequently, a biofilm was allowed to grow on the voice prostheses over 3 days. On day 4 the device was perfused with phosphate buffered saline, pH 7.0, after which the prostheses were left in the moist environment of the drained device. During a period of 12 days the perfusion scheme was repeated 3 times a day. At the end of the day the artificial throat was filled with growth medium for 30 minutes and left to drain overnight.

Monitoring of biofilm formation

The transparent Plexiglas walls of the device allowed constant monitoring of the process of biofilm formation. The plugs holding the prostheses could be removed for a close-up examination of the flanges without disturbing the colonization process. Special attention was given to the extent and location of the various biofilm deposits on the various parts of the valve mechanisms, while the consequences for valve functioning were determined for each type of voice prosthesis.
Scanning electron microscopy was used to evaluate biofilm formation on the silicone rubber surface of the voice prostheses. On day 12 the voice prostheses were removed from the insertion plug. After removal they were flushed twice (sucrose 6.8% in 0.1 M cacodylaat buffer pH 6.8) for a period of 30 seconds. Afterwards the prostheses were pre-fixated in a solution of glutaraldehyde 2% and 0.1 M cacodylate buffer. Post-fixation was performed by using a reduced TAO (tannic acid-arginine-OsO_4, Osmium) procedure. After fixation the specimens were step dehydrated twice (30-50-70-80-90-100% ethanol) for 1 hour and critical point dried with CO_2. This procedure was followed by coating the material with a thin layer of gold(5 nm) (Ion Beam Sputter, Oxford Cryo). Low voltage scanning electron microscopy (SM-6301F, JEOL) was performed with different working distances and angles at 2 kV.

Results

After 12 days successful development of biofilms on the esophageal flange of the examined voice prostheses was observed. Macroscopically, the deposits on the esophageal flange were similar to those seen on dysfunctional prostheses in patients. Scanning electron micrographs demonstrated representative deposits which were solidly adhered to the material and could not be flushed away. During perfusion of the flow-chambers, spontaneous leakage of fluids through the prostheses was also observed. This is dependent on the amount of accumulation of th deposits around the valve and the valve-seating.

In figures 3a and 3b scanning electron micrographs of the Groningen prosthesis are shown with diffuse deposits on the esophageal flange. Also, deposits are evident on the edge of the slit valve which will ultimately interfere with closure.

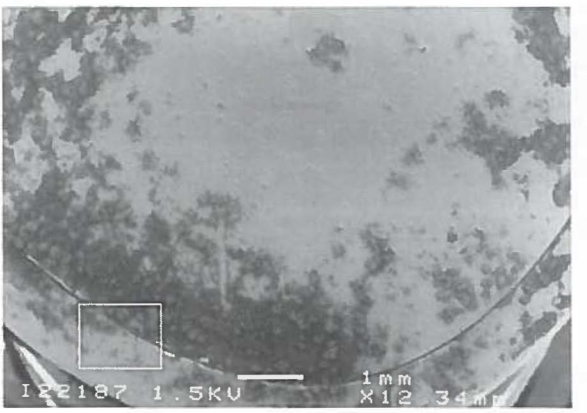

Figure 3a

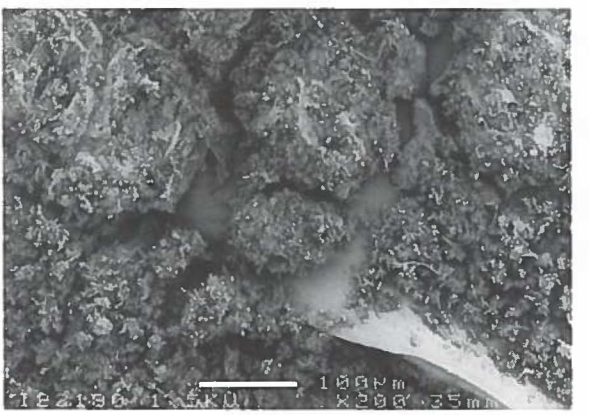

Figure 3b

Figure 3. Deposits on the hat of the esophageal flange (a) of a Groningen low-resistance prosthesis. The marked area is magnified in (b) in which obstruction of the semicircular slit valve with insufficient valve closure is shown. The bar equals 1mm for the low magnification (a) and 100 µm for the high magnification (b).mulation of the deposits around the valve and the valve-seating.

Overall, comparable changes to the esophageal flanges of the Provox2 and Blom-Singer devices were observed (Fig. 4a-b and 5a-b).

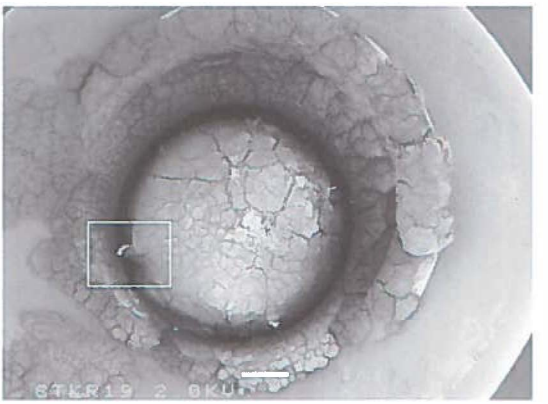

Figure 4a

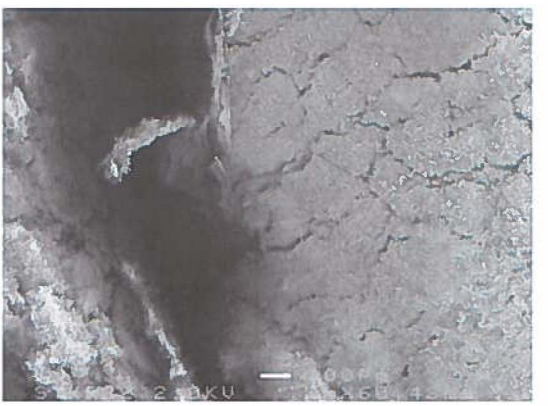

Figure 4b

Figure 4. Illustrations of the recessed hinged valve of the Provox2 prosthesis with deposits at both the esophageal flange and valve recess (a). The marked area is magnified in (b) with deposits at the valve seating which interrupts proper valve closure. The bar equals 1mm for the low magnification (a) and 100 µm for the high magnification (b).

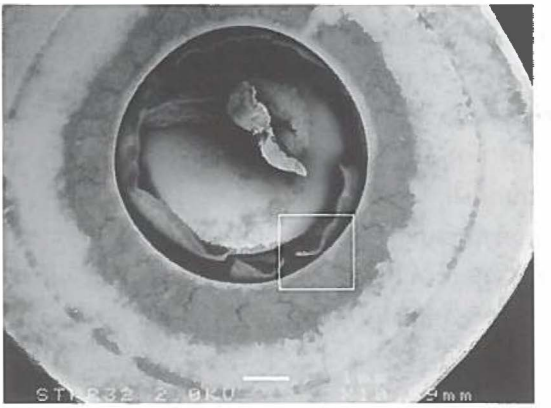

Figure 5a

Figure 5b

Figure 5. Illustrations of the recessed hinged valve of the Blom-Singer prostheses demonstrating the same as in figure 4, deposits at both the esophageal flange and valve recess (a). The marked area is magnified in (b) with deposits at the valve seating which interrupts proper valve closure. The bar equals 1mm for the low magnification (a) and 100 µm for the high magnification (b).

However, these prostheses provided with a hinged valve design with an almost 360 degrees angle were relatively more profoundly disturbed by the circumferential colonization of the valve seating, which interfered directly with valve closure. The smaller surface of the flap valves of the Provox2 and Blom-Singer prostheses are less colonized compared to the Groningen device. The shape of the esophageal flange may also contribute to the accumulation of deposits at the site of recesses and protruding parts. In the closed position, the hinged

valves of the Provox2 and Blom-Singer prostheses are not in level with the actual esophageal flange, but are situated in a niche with or without a small hood. These niches can by considered as potential sites for biofilm formation, since the shearing forces exerted by the esophageal movements
and contents on these sites are minimal.
As shown in figures 6a-b the esophageal flange structures of the VoiceMaster prosthesis are diffusely colonized by biofilms, including the surface of the titanium valve seating and sleeve. Remarkably, the star shaped tripod which

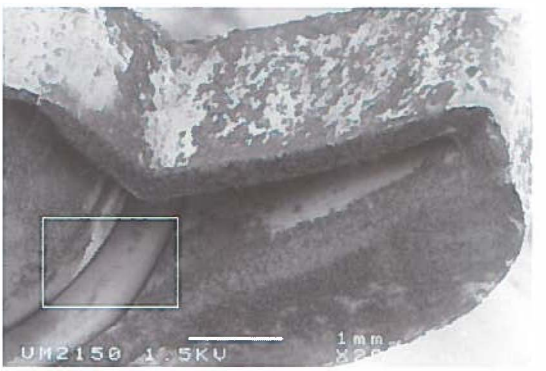

Figure 6a

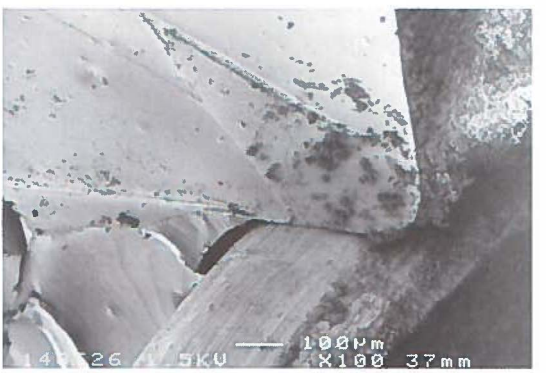

Figure 6b

Figure 6. Diffuse colonization of the tripod structure of the VoiceMaster prosthesis is shown (a). The marked area is magnified in (b): a sliced section of the silicone rubber cast surrounding the titanium sleeve is illustrated. Biofilm formation on the silicone rubber edges and the inner surface of the titanium shaft is clear. The bar equals 1mm for the low magnification (a) and 100 µm for the high magnification (b.)

supports the ball valve part during opening and closure was heavily colonized and showed deterioration of the silicone rubber arms. Diffuse deposits were noticed along the edges of the titanium sleeve and the silicone rubber cast, resulting in deformation of the edges at the valve seating.

Discussion

The development of several types of voice prostheses has basically been focused on the improvements of the aerodynamic properties of the device by designing a low-resistance one-way valve. However, the success of tracheo-esophageal speech acquisition not only depends on merely prosthesis-related factors, but also on patient-related factors which may affect the functioning of the valve system in the pharyngoesophageal environment. Further improvements on the method of tracheoesophageal speech should be concentrated on critical design features of voice prostheses to increase the device life time. In this study *in vitro* developed biofilms in a artificial throat were highly comparable to the biofilms obtained from explanted prostheses *in vivo*.[12] All tested prostheses are prone to biofilm formation, which will interfere with their basic functions and refined aerodynamic properties. However, each design showed to have specific predilection sites for colonization. Overall, the crucial sites are the valve edges where microbial growth and accumulation of deposits will interfere with valve closure. These sites are difficult to reach during normal maintenance with the prosthesis in situ. The surface dimensions of the valve parts are likely to determine the increase of airflow resistance since the accumulation of deposits on the esophageal surface will lead to increased weights and stiffened material properties. The Groningen low-resistance voice prosthesis has known aerodynamic properties which are less favorable compared to flap or ball valved prostheses.[16] The valve of the Groningen prosthesis consists of a semi-circular slit in the hat of the esophageal flange. Opening of the valve requires bending of the convex flange structure which has an large surface area compared to the total esophageal flange surface area. The large esophageal valve surface of the Groningen prosthesis usually carries huge amounts of deposits. The subsequent deterioration of the

silicone rubber surface by microbial ingrowth will influence the specific properties of the material and may lead to decreased flexibility, thus troublesome valve opening and increased airflow resistance. The typical semi-circular slit-valve opening will be further decreased by biofilm formation as observed clinically and in the artificial throat. Secondary, leakage through the prosthesis will occur due to blockage and deformation of the esophageal hat leading to inappropriate valve closure.[17-19] In contrast, prostheses with a hinged valve allow an easier opening of the trapdoor with a wider opening angle. The valve surface area is relatively smaller, but the relative valve seating area is larger, which allows more biofilm formation at this site. The Blom-Singer and Provox2 prostheses equipped with a flap valve are more frequently replaced due to internal leakage, but rarely due to increased phonatory efforts and airflow resistance. This can be explained by the valve design which is sensitive for biofilm formation at the valve seating, which is also not in level with the surrounding esophageal flange.

Technically the VoiceMaster ball valved prosthesis has maximal airflow capacities at the esophageal site, but is most likely to cause valve closing pro-blems due to the available circular valve seating at the site of the titanium sleeve as well as around the ball valve. The ball valve will be colonized ra-pidly, while the star shaped tripods are affected as well. This may interfere with both the opening and closure of the valve mechanism. The star shaped esophageal flange construction is also prone to accumulation of various debris. Even the titanium sleeve surface is not withheld from colonization, as is known from studies related to the plaque formation on endosseous titanium.[20,21] Bothersome, the borders of the sleeve and the surrounding silicone rubber shaft and flange allows ingrowth of yeasts which will ultimately lead to irreversible damage of the valve seating. In vivo, these sites are not accessible for cleansing.

Based on these findings prosthesis dysfunction due to valve failure is determined by colonization of the esophageal flange and deterioration of the silicone rubber components, which will interfere with appropriate valve closure and opening. The failure risk of each design depends on the dimensions of the contact area between the valve and its seating, the surface area of the actual valve part, the construction of the pivoting points, and the surrounding

niches and other esophageal flange structures which allow the built-up of deposits. Replacements due to high airflow resistance are typical for large valve surfaces which allow rapid and huge colonization of the esophageal site of the prosthesis. Although leakage of fluids may be absent, the increased phonatory efforts will be troublesome and will necessitate valve replacement.[3,16] Besides the mass effect of the deposits, the flexibility of the silicone rubber components will be affected too. These effects can provoke both insufficient closure as well as difficult opening of the valve.

Finally, we conclude that the artificial throat is an effective system for *in vitro* research of silicone rubber voice prostheses. In this system various influences on the structure and function of prosthetic devices can be studied. This study definitely showed that device life is primarily dependent on the biofilm formation. This makes the artificial throat extremely useful because it allows us to study the effects of single factors on the colonization process. These laboratory studies precede more comprehensive clinical trials to evaluate modified prosthetic devices and therapeutic interventions on the colonization process.

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Chapter 7

THE EFFECT OF BUTTERMILK CONSUMPTION ON BIOFILM FORMATION ON SILICONE RUBBER VOICE PROSTHESES IN AN ARTIFICIAL THROAT

Busscher HJ, Bruinsma G, Van Weissenbruch R, Leunisse C, Van der Mei HC, Dijk F, Albers FWJ. The effect of buttermilk consumption on biofilm formation on silicone rubber voice prostheses in an artificial throat. Eur Arch of Otorhinolaryngol 1998; 255:410-413.

Introduction

Voice rehabilitation using voice prostheses after laryngectomy is generally considered to be superior to esophageal speech.[8] However, as a drawback prostheses become colonized within several days to months by a thick biofilm that eventually causes leakage or blockage of the valve.[9,12] As a consequence indwelling silicone rubber voice prostheses commonly have to be replaced on average every 4 months.[14]

Different approaches have been undertaken to delay biofilm formation on indwelling silicone rubber voice prostheses. These include modification of the silicone rubber surface, oropharyngeal decontamination by consumption of amphotericin B lozenges and buccal bioadhesive slow-release tablets containing miconazole nitrate.[5,11,15] So far, silicone rubber surface modification has yielded disappointing results, although chemisorption of compound with low surface free energy and mobile long chain fluorocarbons may prove useful clinically.[6] Chemoprophylaxis has produced some increase in the lifetime of indwelling voice prostheses but biofilms still continue to form and increase in size since their formation in silicone rubber protects microorganisms against environmental attacks.[2,3] In previous studies *Candida albicans* grown in a biofilm was approximately five times more resistant to various clinically useful antifungal agents than planktonic cells.7 Additionally, long-term use of antifungal agents bears the risk of inducing resistant strains even if patient compliance is excellent. Recently, yeast strains resistant to fluconazole have been described.[4]

Within patient support groups in The Netherlands, laryngectomees have suggested that the consumption of buttermilk not only prolongs the clinical usefulness of indwelling silicone rubber voice prostheses but can also resolve early leakage of dysfunctioning valves. Extension of the lifetime of indwelling silicone rubber voice prostheses from several months to 1 year through the consumption of buttermilk has been mentioned in the support, group magazine *The Second Voice*. Scientific evidence for a potential beneficial effect of buttermilk consumption is lacking and probably impossible to obtain from clinical studies due to the necessary duration of such studies, during which factors related to environmental and patients' life styles are hard to control.

The aim of the present study was to investigate whether the consumption of buttermilk by laryngectomees may have a true inhibitory effect on the formation of a biofilm on silicone rubber voice prostheses. To this end, experiments were carried out in a recently developed artificial throat in which Groningen button voice prostheses were placed.[10]

Materials and methods

"Low-resistance" Groningen button voice prostheses were kindly provided by Medin Instruments and Supplies (Groningen, The Netherlands) and placed in two transparent modified Robbins devices that were recently described as an "artificial throat.[10] These are shown schematically in figure 1.

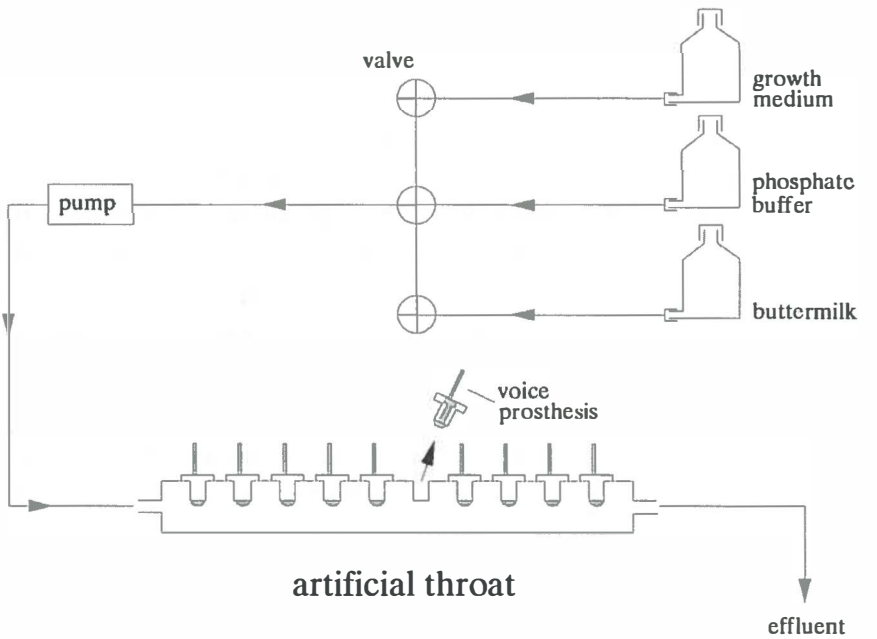

Figure 1. Schematic presentation of the artificial throat set-up, equipped with ten Groningen Low Resistance voice prostheses, as recently described in detail by Leunisse et al.[10]

Each artificial throat was equipped with ten Groningen button voice prostheses. The total cultivable microflora from an explanted Groningen button voice prosthesis, containing a variety of yeast and bacterial strains among which *Candida albicans, Candida tropicalis,* streptococcal and staphylococcal strains, were cultured in a mixture of 30% brain heart infusion broth (Oxoid, Basingstoke, UK) and 70% defined yeast medium (per liter: 7.5 g glucose, 3.5 g (NI-14)2S04, 1.5 g L-asparagine, 10 Ing L-histidine, 20 Ing DL-methionine, 20 Mg DL-tryptophane, 1 g KI-12P04. 500 mg M9S04.71-1,0, 500 mg NaCI, 500 mg CaCh. 2HO, 100 mg yeast extract, 500 pg H3B03, 400 pg ZnSW 7H,O, 120 -Lg Fe(I11)0, 200 pg Na2M004.2WO, 100 pg KI, 40 pg CUS04.51-1,0) and used to inoculate the artificial throats. Subsequently, a biofilm was allowed to grow on the voice prostheses in both artificial throats during 3 days by refreshing the devices each day with growth medium. On the 4th day, the artificial throats were both flushed with 10 mM phosphate buffer (pH 7.0) to remove remnants of the growth medium.

In one artificial throat, serving as the simulated control group, 700 ml triphosphate buffer was perfused through the device and the prostheses were left in the moist environment of the drained modified Robbins device. In the other artificial throat the daily consumption of buttermilk was simulated by perfusing it with 700 mI fresh buttermilk (Melkan, C.I.V. Superunie B.A., Vianen, The Netherlands). To remove remnants of buttermilk, phosphate buffer was perfused through the device, after which it was left drained. This perfusion scheme was repeated three times a day. During the night, both artificial throats were filled with growth medium, which was removed promptly each morning by flushing with phosphate buffer prior to the next perfusions. Both experiments were continued for 8 days at room temperature and the tracheal sides of the prostheses were left in ambient air without taking precautions to prevent contamination from the air, similar to the clinical situation with a stoma. At intervals of 2-3 days, prostheses were removed from random positions in the artificial throats for scanning electron microscopy and replaced by dummies.

RESULTS

Scanning electron micrographs of Groningen button voice prostheses removed from the control group demonstrated heavy biofilm formation that extended over a major part of the valve (Fig. 2), with clear ingrowth of microcolonies (Fig. 3).

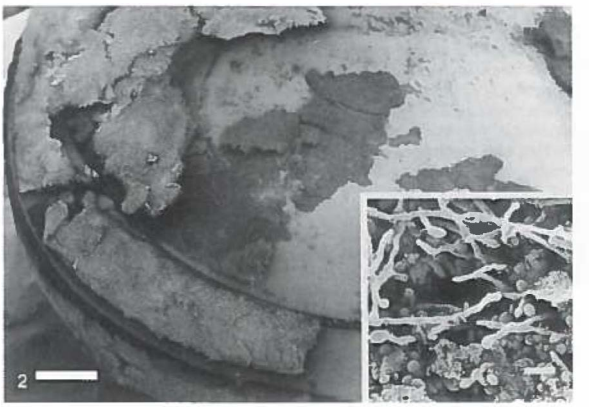

Figure 2. Scanning electron micrograph of a control Groningen voice prosthesis removed from the artificial throat after 7 days. A heavy biofilm formation is present. The bar equals 1 mm for low magnification micrograph and 10 µm for the inset.

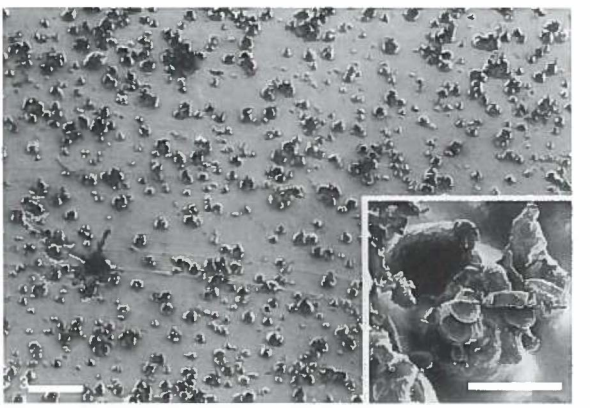

Figure 3. Scanning electron micrograph of a control Groningen voice prosthesis removed from the artificial throat after 7 days. Ingrowths of microcolonies have produced deterioration of the silicone rubber. The bar equals 100 µm for the low magnification micrograph and 10 µm for the inset.

In contrast, scanning electron micrograph findings of the Groningen button voice prosthesis after simulated buttermilk consumption showed that the entire esophageal side of the prosthesis was virtually clean (Fig. 4).

Figure 4. Scanning electron micrograph of a control Groningen voice prosthesis removed from the artificial throat following daily simulation of buttermilk consumption. Virtually no biofilm formation is present. The bar equals 1 mm.

Discussion

Our present experiences are based on use of the artificial throat to demonstrate the effects of daily buttermilk consumption on biofilm formation on indwelling silicone rubber voice prostheses. The biofilms formed in our control group of prostheses had a remarkable similarity to the biofilms formed in vivo.[13] The ingrowth phenomena observed in our prostheses were already in a more advanced state than observed in a modified Robbins device equipped with silicone rubber disks and inoculated with yeasts only.[12] This likely indicates that attempts to prevent biofilm formation on voice prostheses should not necessarily focus on colonization with yeasts only, but with colonizing bacteria as well, since there appears to be a definitive role for bacteria in maintaining the biofilm.[15]

The simulated consumption of buttermilk in the artificial throat almost fully prevented biofilm formation on our prostheses over a time scale of at least 8

days, thereby confirming anecdotal suggestions amongst laryngectomees that buttermilk was definitely useful clinically. The mechanism by which the consumption of buttermilk interferes with biofilm formation on voice prostheses can only be speculated upon. The following description of buttermilk is generally valid for all available products. Buttermilk is a mildly acidic dairy product with a pH of 4.5 due to the fermentation of sugars into lactic acid by *Lactococcus lactis* and *Streptococcus cremoris* and contains a number of enzymes in addition to a high calcium content (110- 120 mg/ 100 g). *L. lactis* strains are known to release antimycotic substances, while the proteins pre-sent in buttermilk include casein, lactoglobulin and immunoglobulins and may have detergent properties.[11] Obviously, the combined effect of all pro-perties of buttermilk contributes to the control of biofilm formation on indwelling silicone rubber voice prostheses. Similar effects on biofilm formation on indwelling voice prostheses have been suggested to result from the consumption of Turkish yoghurt, a beverage with active *Streptococcus thermophilus* and *Lactobacillus bulgaricus.*

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Chapter 8

SUMMARY AND CONCLUSIONS

Summary

Total laryngectomy as an important treatment modality in laryngeal cancer always results in the loss of normal vocal function. Restoration of the vocal functions following laryngectomy continues to be a major challenge. Esophageal speech and mechanical speech by using electric larynges are know as primary methods of alaryngeal communication. Nowadays, tracheoesophageal speech with a primarily inserted silicone rubber voice prosthesis is regarded as the surgical method of choice for speech restoration after total laryngectomy. As a result of the ongoing successes various types of tracheoesophageal voice prostheses have been developed on basis of a one-way valved biflanged device. The main drawback of these devices is the limited device life, due to biofilm formation on the prosthesis and subsequent deterioration of the silicone rubber material of the devices.
In this thesis a series of subsequent clinical and experimental investigations are described on the functional and structural aspects of frequently used indwelling voice prostheses in order to identify the most relevant factors with regard to the quality and life time of the voice prostheses.

In Chapter 2 a review of several aspects of total laryngectomy in relation to the different methods of vocal rehabilitation after total laryngectomy is given.

In chapter 3 the results of retrospective study on 102 postlaryngectomy patients are described. This study was performed in order to determine and compare the survival time and indications for replacements of the Groningen Low Resistance and the Provox2 voice prostheses. In this patient cohort a total of 712 prosthesis were inserted. Comparing both groups of voice prosthesis, the Groningen Low Resistance prosthesis had a longer mean *in situ* lifetime (132 days) than the the Provox2 prosthesis (70 days). Statistical analysis of the mean *in situ* lifetime per patient showed no significant differences between the two types of prosthesis under investigation. Leakage of salivary contents and food through the prosthesis occurred significantly more often with the Provox2 prosthesis. On the other hand complaints of increased

effort to speak was observed significantly more often with the Groningen Low Resistance voice prosthesis. The results of this study underline the importance of detailed analysis of the behaviour of the tracheo-esophageal shunt prostheses in relation to inter- and intraindividual variables.

In Chapter 4 the aerodynamic properties of 6 different tracheo-esophageal voice prostheses in a standardized laboratory setting are described. To measure the transdevice air pressure loss (kPa) at various transdevice air flow rates (l/s) a customized experimental setup was used. The most commonly used devices in Europe and the United States were subject of investigation: Blom-Singer Gelcap indwelling low resistance, Groningen Low Resistance, Groningen Ultra Low Resistance, Provox, Provox2 and the VoiceMaster prostheses. The experiments were performed using normal dry air and fully saturated warm air. The Groningen Ultra Low Resistance, Provox, Provox2 and the VoiceMaster prostheses showed the lowest transdevice air resistance. Comparison of transdevice airflow resistance revealed obvious differences between the normal dry and the saturated warm air measurements. In all prostheses, except the VoiceMaster voice prosthesis, the transdevice air resistance was significantly lower during saturated warm air measurements. Although all examined silicone voice prostheses are claimed to be low resistance devices, significant differences in transdevice air resistance exist. Determination of the aerodynamic characteristics should be performed by choosing specific laboratory conditions which resemble the *in vivo* situation.

In chapter 5 the development of the artificial throat is presented. Further understanding of the process of development and inhibition of the colonization of these polymer surfaces of silicone rubber voice prostheses requires several comprehensive clinical studies. However, *in vivo* research of the biomaterials of the voice prostheses is difficult and time consuming. In order to simulate the natural process of biofilm development under dynamic nutrient conditions, an artificial throat was developed. Biofilm developed on Groningen button voice prostheses *in vitro* could not be distinguished from that formed over several months *in vivo*. This method can be used as a standardized approach for studying functional and structural aspects of all com-

mercially available indwelling and non-indwelling voice prostheses including the Groningen button, Provox, VoiceMaster, Blom-Singer and other devices under various laboratory conditions.

In Chapter 6 an analysis of biofilm formation on 4 different low resistance tracheo-esophageal voice prostheses in respect to valve dysfunction is described. The natural process of biofilm development under dynamic nutrient conditions was simulated in a modified Robbins device to evaluate the biofilm-related valve dysfunction of the Groningen, Provox2, Blom-Singer indwelling, and VoiceMaster voice prostheses. Obstruction of the semicircular slit-valved prostheses Groningen prosthesis leading to increased airway resistance was not only caused by a built-up of deposits on the esophageal flange and valve hat, but also by accumulation of deposits on the semicircular valve seating. The hinged valved Provox2 and indwelling Blom-Singer prostheses failed to sufficiently close the valve due to biofilm formation on the valve seating. The esophageal flange of the VoiceMaster prosthesis was affected, but the tripod structure of the ball valve was fully colonized up to the titanium sleeve, which interferes with proper valve opening and closure.
In this study valve dysfunction is demonstrated to be primarily related to the biofilm formation, but the specific primary reasons for replacement depended largely on the valve design. These findings could be used for the further development and modification of voice prostheses to facilitate tracheoesophageal speech.

In chapter 7 the influence of buttermilk on the colonization of the Groningen voice prosthesis was studied. Biofilm formation on indwelling silicone rubber voice prostheses in laryngectomized patients is still the main reason for dysfunction of the valve, leading to frequent replacements. Within patient support groups in The Netherlands, laryngectomees have suggested that the consumption of buttermilk prolongs the lifetime of indwelling silicone rubber voice prostheses. The aim of the present study was to evaluate the influence of buttermilk on biofilm formation on Groningen Low Resistance voice prostheses in the artificial throat. Ten prostheses were placed in a simulated control group and ten other prostheses in a group with a simulated consumption

of 700 ml buttermilk three times a day. Biofilms were allowed to grow on the prostheses by inoculating two artificial throats with the total cultivable microflora (bacteria and yeasts) isolated from an explanted Groningen voice prosthesis. After 3 days, one artificial throat was perfused three times daily with phosphate buffer (control group) for 8 days, while the other artificial throat was perfused with buttermilk. Prostheses removed from the artificial throat in the control group were covered with a thick biofilm. Scanning electron microscopy showed microcolonies growing into the silicone rubber, similar to the ingrowth observed on explanted Groningen voice prostheses. The simulated consumption of buttermilk in the other artificial throat almost fully prevented the formation of a biofilm on the prostheses during the experimental period. These in vitro experiments in the artificial throat demonstrate that the deterioration of voice prostheses can be limited by the daily intake of buttermilk through its inhibitory effects on biofilm formation.

Conclusions

One of the major consequences of total laryngectomy is the loss of speech. In the recent decades vocal rehabilitation has been subject of substantial clinical and experimental research resulting in the tracheoesophageal speech as the current restoration modality of choice. The last 15 years voice rehabilitation with silicone rubber tracheoesophageal voice prostheses has undergone major changes. The introduction of low resistance prostheses has further facilitated tracheoesophageal speech. Although this development has contributed to considerable improved quality of life, several restrictive factors of tracheoesophageal shunt speech remains. These restrictions can be divided into prostheses-related and patient-related factors. The prosthesis-related factors can be studied by thorough *in vitro* research and clinical studies. Performing *in vitro* research of functional and structural aspects of tracheo-esophageal voice prostheses, the *in vivo* circumstances have to be simulated as close as possible. Under specific laboratory conditions the mechanical and aerodynamic properties of voice prostheses can be successfully examined and compared. With the artificial throat it is possible to simulate biofilm formation and subse-

quent deterioration of the prostheses. The system of the artificial throat can be modified to imitate numerous *in vivo* conditions, which allow us to study the effect of single factors on the colonization process. Also the application of tracheo-esophageal shunt prostheses in a clinical setting needs to be evaluated over a longitudinal period of time. Such an evaluation should not only include aspects with regard to the speech quality and quantity, but also investigate the insertion method, *in situ* life time of the device, the reasons for replacements and the cost-effectiveness.

To learn more about the patient-related factors of tracheoesophageal shunt speech, which are not present in an *in vitro* situation, prospective clinical studies have to be performed. In general such studies are complex and time consuming. The resulting data of previous *in vitro* research can be helpful to further conduct these comprehensive clinical trials. At this moment a total implantable artificial larynx seems to be far away, while the implementation of larynx transplantation has immunological and oncological drawbacks, further improvements on the method of tracheoesophageal shunt speech should be pursuited. Therefore future developments should be directed to measures preventing biofilm formation on tracheoesophageal voice prostheses. Based upon contemporary research influencing the oral and esophageal microflora with specific dietary and or salivary supplements or adjustment are possible opportunities. Also, material and design modifications of the voice prosthesis will play an important role in this process. Reaching these future developments adequate clinical follow-up including patient history and information on dietary intake, salivary production and changes will be necessary to assess. Suggestions made by patients support groups can also be contributing and be implemented in research projects to come to improve vocal rehabilitation with tracheoesophageal voice prostheses.

Samenvatting en conclusies

Samenvatting

Kwaadaardige aandoeningen van het strottehoofd (= larynx) zijn betrekkelijk zeldzaam. Tegenwoordig kunnen vele van deze aandoeningen succesvol worden behandeld. Helaas heeft de behandeling van deze aandoeningen soms verstrekkende gevolgen voor de desbetreffende patiënt. Bij uitgebreide vormen van kanker van het strottehoofd of bij het terugkeren van de aandoening, bijvoorbeeld na een bestralingsbehandeling, zal het strottehoofd in zijn geheel operatief moeten worden verwijderd. Een dergelijke chirurgische verwijdering van het strottehoofd wordt een laryngectomie genoemd. Doordat de stembanden een cruciaal onderdeel zijn van het strottehoofd, zal de patiënt zijn natuurlijke geluidsbron voor de normale stem verliezen. Dit heeft grote consequenties voor het functioneren van de patiënt, omdat naast de stem ook het slikken en ademen drastisch zal veranderen. De ernst van deze handicap werd al van af de eerste laryngectomie door Billroth in 1873 onderkend. In voorbereiding op deze ingreep werd een kunstventiel bij honden ontwikkeld, dat bij deze patiënt met goed resultaat werd ingebracht. Sindsdien werden diverse pogingen voor spraakrevalidatie na een laryngectomie ontwikkeld en beproefd.

Tegenwoordig zijn er drie vormen spraakrevalidatie beschikbaar, nl. de (electromechanische) kunstlarynx, slokdarmspraak en slokdarmspraak met behulp van ventielprothesen (= tracheo-oesofageale shunt spraak). Bij de mechanische spraakrevalidatie m.b.v de kunstlarynx, wordt gebruik gemaakt van een los apparaat dat geluid gegenereerd op basis van elektromechanisch trillingen. Het apparaat kan tegen de hals of mondbodem worden gehouden, waarna het geluid van de uitwendige bron via de huid naar de mondholte wordt voortgeleid. De daadwerkelijke stem en spraakvorming vindt plaats via de resterende structuren in de keel en mondholte, die normaal gesproken betrokken zijn bij de articulatie. Het nadeel van deze kunstlarynx is dat de spraak vrij monotoon klinkt en erg opvalt. Bij de slokdarmspraak wordt

lucht vanuit de mondholte de slokdarm ingebracht. Vanuit de slokdarm wordt de ingebrachte lucht als het ware opgeboerd naar de mondholte en keel. Ter hoogte van de slokdarmingang wordt het slokdarm geluid gepro-

duceerd. De plaats waar het geluid wordt gegenereerd wordt het faryngo-oesofageale segment (=PE-segment) genoemd. Op deze manier wordt een meer natuurlijk stemgeluid geproduceerd. Het nadeel is echter dat de slokdarmspraak over het algemeen moeilijk wordt aangeleerd. Verder is het stemgeluid relatief zacht en kunnen alleen korte zinnen worden gevormd door telkens lucht in te nemen. Tracheo-oesofageale shuntspraak met behulp van ventielprothesen is op dit moment de meest gebruikte revalidatiemethode. De prothese wordt in een verbindingskanaal tussen de luchtpijp en de slokdarm geplaatst. Dit kanaal oftewel fistel wordt chirurgisch aangelegd. De ventielprothese heeft een klepje, dat passage van uitademingslucht vanuit de luchtpijp naar de slokdarm mogelijk maakt. Tegelijkertijd voorkomt deze klep lekkage van vocht en voeding vanuit de slokdarm naar de luchtpijp. Door de opening van de luchtpijp naar de hals (tracheostoma) met een vinger af te sluiten, kan de patiënt lucht uit de longen door de ventielprothese heen blazen. Deze luchtstroom zal vervolgens net als bij de slokdarm spraak, het weefsel ter plaatse van het PE-segment in trilling brengen en geluid produceren. De longen hebben een veel grotere luchtvoorraad waardoor er langere zinnen kunnen worden gemaakt.
De eerste ventielprothese, ontwikkeld door Singer en Blom in de Verenigde Staten in 1979, had de vorm van een 'eendenbek'. De prothese moest vrijwel dagelijkse worden gereinigd door de patiënt. Later werden er prothesen ontwikkeld, die langere tijd in konden blijven en onderhoudsvriendelijker waren. Over het algemeen zijn deze lange verblijfsprothesen gemaakt van siliconenrubber. Dit materiaal wordt goed door het lichaam geaccepteerd en kan makkelijk worden gevormd. Het nadeel van siliconenrubber is dat het snel overgroeit raakt door bacteriën, schimmels en gisten uit de mondholte. Dit proces wordt kolonisatie genoemd. Deze micro-organismen gaan zich op de prothese vermenigvuldigen en zorgen ervoor dat er na verloop van tijd een beslag (=biofilm) op met name het klepmechanisme van de prothese ontstaat. De biofilm kan het klepmechanisme aantasten, waardoor de prothese kan gaan lekken. Ook kan de prothese verstopt raken waardoor de spraak moeizaam of zelfs onmogelijk wordt door de verhoogde luchtweerstand. De verblijfsprothesen hebben een gemiddelde levensduur van 3 tot 5 maanden. Zodra het klepmechanisme het laat afweten moet een prothese door een

KNO-arts worden vervangen. Dit wordt door patiënten vaak als lastig ervaren, vooral als dit vaak moet plaatsvinden.

In dit proefschrift worden een aantal experimenten bij patiënten (=*in vivo* of klinisch onderzoek) als in het laboratorium (=*in vitro* onderzoek) beschreven. De onderzoeken hebben betrekking op specifieke aspecten van het werkingsmechanisme van de prothesen, de groei van micro-organismen op het materiaal, en mogelijkheden om dit te beïnvloeden.

In hoofdstuk 2 wordt een overzicht gegeven van de kwaadaardige aandoening van het strottehoofd, de behandelingsmogelijkheden en de methoden van spraakrevalidatie .

In hoofdstuk 3 worden de medische gegevens van 102 patiënten die een laryngectomie hebben ondergaan beschreven. Dit onderzoek werd gedaan om de levensduur en redenen voor vervangen van twee verschillende verblijfsprothesen, namelijk de Groningen Low Resistance en de Provox2 spraakprothesen, te evalueren en te vergelijken. In de onderzochte groep patiënten werden in het totaal 712 prothesen verwisseld. Een vergelijking van de levensduur van beide prothesen toonde aan, dat de Groningen Low Resistance prothese een langere gemiddelde verblijfsduur (132 dagen) had in vergelijking met de Provox2 prothese (70 dagen). Na statistische analyse van de gemiddelde verblijfsduur per patiënt kon er echter geen significant verschil worden aangetoond tussen de twee type prothesen. Lekkage van vloeistoffen door de prothese werd wel significant vaker gevonden bij de Provox2 spraakprothesen, terwijl bij de Groningen prothesen juist klachten van verhoogde luchtweerstand bij het spreken significant vaker werd geconstateerd. Deze studie benadrukt het belang van nauwkeurige analyse van de karakteristieken van tracheo-eosofageale ventielprothesen bij diverse patiëntenpopulaties.

In hoofdstuk 4 wordt een beschrijving gegeven van de zgn. aërodynamische eigenschappen van 6 verschillende tracheo-eosofageale ventielprothesen. Dit onderzoek kon worden uitgevoerd door gebruik te maken van gestandaardiseerde laboratoriumomstandigheden. Het weerstandsverval over de prothe-

sen (kPa) bij verschillende luchtstromen (l/s) kon worden bepaald door gebruik te maken van een specifieke meetopstelling. De meest gebruikte type spraakprothesen in Europa en de Verenigde Staten werden getest, met name de Blom-Singer indwelling low-pressure (Gelcap), de Groningen Low Resistance, de Groningen Ultra Low Resistance, de Provox, de Provox2 en de VoiceMaster prothese. De experimenten werden zowel uitgevoerd met droge lucht bij kamertemperatuur als met verwarmde vochtige lucht. Bij de Groningen Ultra Low Resistance, Provox, Provox2 en de VoiceMaster prothese werd de laagste luchtweerstand gemeten. De luchtstroomweerstand met normale droge lucht liet een duidelijk verschil zien in vergelijking met warme vochtige lucht. De luchtstroomweerstand over de prothese was bij alle prothesen met uitzondering van de VoiceMaster significant lager bij de metingen waarbij gebruik werd gemaakt van warme vochtige lucht. Ondanks het feit dat alle onderzochte spraakprothesen behoorden tot het type lage weerstandsprothese, bestonden er significante verschillen in luchtstroomweerstand waarden tussen de prothesen onderling. Het bepalen van de aërodynamische eigenschappen van spraakprothesen dient te worden uitgevoerd onder laboratoriumomstandigheden, die de klinische situatie zo nauwkeurig mogelijk benaderen.

In hoofdstuk 5 wordt de ontwikkeling van een kunstkeel belicht. Om tot een beter begrip van het kolonisatieproces van het oppervlak van spraakprothesen te komen, zullen veelomvattende klinische studies noodzakelijk zijn, maar deze studies zijn vaak moeilijk uitvoerbaar en nota bene tijdrovend. Om het natuurlijke proces van biofilmvorming onder verschillende voedingsomstandigheden te kunnen onderzoeken, werd een kunstkeel ontwikkeld op basis van het principe van een gemodificeerde Robbins buis. De biofilm die op deze manier op Groningen spraakprothesen werd gevormd, kon niet worden onderscheiden van de biofilm op prothese die enkele maanden bij patiënten geïmplanteerd was. Deze methode kan dus worden gebruikt als standaard voor het bestuderen van biofilm op diverse protheses om nader onderzoek te doen naar diverse functionele en structurele aspecten.

In hoofdstuk 6 wordt wederom de biofilmvorming op 4 verschillende lage weerstand tracheo-oesofageale spraakprothesen bestudeerd, waarbij er vooral gelet is op het design van het klepmechanisme en de specifieke gevoeligheid hiervan. Er werd wederom gebruik gemaakt van de kunstkeel. Vervolgens werd de biofilm op de prothese in relatie tot het disfunctioneren van de klep onderzocht. Dit werd gedaan voor de Groningen Low Resistance, Provox2, Blom-Singer indwelling low-pressure (Gelcap) en de VoiceMaster spraakprothesen. Obstructie van de Groningen prothese met een spleetvormige klepmechanisme veroorzaakt in eerste instantie een verhoogde luchtstroomweerstand. Dit werd niet alleen veroorzaakt door opeenhoping van biofilm op de oesofageale flens en de klep van de prothese, maar ook door het beperken van de klepopening ter plaatse van het distale deel van de schacht. Het klapdeur mechanisme van de Provox2 en de indwelling Blom-Singer prothesen faalde door niet afdoende te sluiten ten gevolge van biofilmvorming op de plaats waar de klep sluit. De oesofageale flens van de VoiceMaster prothese was volledig aangetast, waarbij de driepoot structuur van het klepmechanisme in zijn geheel was gekoloniseerd met microorganismen hetgeen doorliep tot aan de titanium schacht. Dit verhinderde dat het klepmechanisme afdoende kon openen en sluiten.
In deze studie werd aangetoond dat het disfunctioneren van het klepmechanisme van tracheo-oesofageale spraakprothesen primair verband houdt met biofilm vorming, waarbij de specifieke redenen van verwisselen grotendeels afhankelijk is ontwerp van het klepgedeelte van de prothese.

In hoofdstuk 7 wordt de invloed van karnemelk op de kolonisatie van Groningen spraakprothesen bestudeerd. Biofilmvorming op het siliconenrubber van spraakprothesen bij patiënten na een laryngectomie is nog steeds de belangrijkste oorzaak voor het falen van het klepmechanisme, hetgeen leidt tot het regelmatige verwisselen van deze prothesen. Binnen de Neder-landse Patiënten Vereniging voor Gelaryngectomeerden werd de suggestie geopperd, dat de consumptie van karnemelk de levensduur van siliconenrubbere spraakprothesen zou kunnen verlengen. Het doel van dit onderzoek was het evalueren van de invloed van karnemelk op de biofilm vorming op de Groningen Low Resistance in de kunstkeel. Tien prothesen werden gebruikt als controle

groep, tien andere prothesen vormden de groep waarbij een driemaal daagse consumptie van 700 ml karnemelk werd gesimuleerd. De twee kunstkelen (een voor de controle en een voor de onderzoeksgroep) werden geënt met de bacteriën en schimmels van de biofilm van een vervangen Gro-ningen spraakprothesen uit een patiënt. Vervolgens werd de vorming van een biofilm op de prothesen in beide kunstkelen gestimuleerd. Na 3 dagen werd een van de kunstkelen driemaal daags gedurende 8 dagen gespoeld met fosfaatbuffer (controle groep), terwijl de andere kunstkeel werd gespoeld met karnemelk. Prothesen die werden verwijderd uit de kunstkeel van de controle groep, waren bedekt met een dikke biofilm. Scanning elektronenmicroscopie liet zien, dat de micro-organismen in het siliconenrubber op identieke wijze groeiden als bij patiënten. De gesimuleerde karnemelk consumptie zorgde ervoor dat biofilmvorming op de prothesen gedurende de onderzoeksperiode bijna in zijn geheel kon worden voorkomen. Deze laboratoriumexperimenten met de kunstkeel tonen aan dat niet alleen de biofilmvorming op spraakprothesen kan worden aangetoond maar ook interventies met een remmend effect op biofilmvorming (zoals karnemelk) kan worden onderzocht.

Conclusies

Een van de belangrijkste gevolgen van een laryngectomie is het verlies van het stem- en spraakvormend vermogen. De afgelopen decennia is er veel klinisch en experimenteel onderzoek gedaan naar verbetering van de spraakrevalidatie na laryngectomie. Deze pogingen hebben ertoe bijgedragen dat de spraakrevalidatie met behulp van tracheo-oesofageale spraakprothesen op dit moment de methode van eerste keuze is. De spraakrevalidatie met behulp van spraakprothesen heeft de laatste 15 jaar belangrijke ontwikkelingen ondergaan. De tracheo-oesofageale spraak is verder verbeterd door de introductie van de zgn. lage weerstandprothesen. Desondanks zijn er nog steeds een aantal beperkende factoren. Deze beperkingen kunnen worden onderverdeeld in prothesegebonden en patiëntgebonden factoren. De prothesegebonden factoren kunnen zowel met in vitro als met in vivo onderzoek nader worden onderzocht. Bij het doen van in vitro onderzoek naar de functionele en

de structurele aspecten van tracheo-oesofageale spraakprothesen, moeten de onderzoeksomstandigheden de klinische situatie goed benaderen. Onder specifieke laboratorium omstandigheden kunnen de mechanische en de aërodynamische eigenschappen van spraakprothesen betrouwbaar worden onderzocht en met elkaar worden vergeleken. Met de kunstkeel is het goed mogelijk om biofilmvorming en aantasting van prothesen te onderzoeken. Het systeem van de kunstkeel kan dusdanig worden aangepast dat diverse omstandigheden, die zich bij de patiënt voordoen kunnen worden gesimuleerd. Het systeem biedt ons de mogelijkheden om het effect van afzonderlijke factoren op het kolonisatieproces te bestuderen. Toch moeten de tracheo-oesofageale spraakprothesen in de kliniek over een langere tijdspanne worden geëvalueerd. Naast de kwaliteits - en kwantiteitsaspecten van de spraak zullen andere aspecten moeten worden betrokken zoals inbrengmethode , de levensduur en de redenen van verwisseling van de prothesen. Tevens lijkt nadere analyse van kosteneffectiviteit in dit kader uiterst relevant.
Om meer te weten te komen over de patiënt gebonden factoren van tracheooesofageale spraak, welke in een in vitro situatie niet aanwezig zijn, zullen prospectieve patiënt gebonden studies moeten worden uitgevoerd. Over het algemeen zijn deze studies complex en tijdrovend. De resultaten van eerder verricht in vitro onderzoek kunnen behulpzaam zijn om zulke ingewikkelde klinische studies beter af te stemmen. Daar een totaal implanteerbaar kunststrottehoofd nog ver weg lijkt en het uitvoeren van een strottehoofdtransplantatie immunologische, oncologische en ethische bezwaren heeft, zullen de komende tijd verdere verbeteringen van de huidige methode van tracheo-oesofageale shuntspraak moeten worden gerealiseerd. Hiervoor zullen maatregelen moeten worden ontwikkeld, die biofilmvorming op spraakprothesen verhinderen. Gebaseerd op hedendaags onderzoek lijkt het beïnvloeden van de microflora met behulp van specifieke dieet en speeksel aanvullingen een positieve bijdragen aan de levensduur van de prothese te kunnen leveren. Ook verbeteringen van het materiaal of het ontwerp van de spraakprothesen kunnen een belangrijke rol spelen in dit proces. Om in de toekomst tot deze ontwikkelingen te komen zal het analyseren van de voorgeschiedenis, de voedingsgewoonte, speekselproductie en klinische ontwikkeling van de patiënt noodzakelijk zijn. Suggesties vanuit patiëntenverenigingen dienen op hun waarde te worden

beoordeeld en kunnen kunnen zelfs in onderzoeksprojecten ter verbetering van spraakrevalidatie met behulp van tracheo-oesofageale spraakprothesen worden geïmplementeerd.

Appendix

Prosthesis type	Manufacturer	Valve design	Materials	Insertion method	Available size
Groningen low resistance	Medin Groningen, The Netherlands	semicircular slit valve (145 °)	silicone rubber	backloading	Length: 5, 7, 9, 11 mm Ø: 7, 8 mm
Groningen ultra low resistance	Medin Groningen, The Netherlands	semicircular slit valve (200 °)	silicone rubber	backloading	Length: 5, 7, 9, 11 mm Ø: 7, 8 mm
Provox	Atos Medical Hörby, Sweden	recessed hinged valve	silicone rubber and radiopaque fluoroplastic valve seating	backloading	Length: 6, 8, 10 mm Ø: 7.5 mm
Provox2	Atos Medical Hörby, Sweden	recessed hinged valve	silicone rubber and radiopaque fluoroplastic valve seating	frontloading and backloading	Length: 6, 8, 10 mm Ø: 7,5 mm
VoiceMaster	Entermed Instruments Woerden, The Netherlands	tripod ball valve	silicone rubber and titanium sleeve	frontloading	Length: 6, 8, 10, 12 mm Ø: 8 mm
Blom Singer indwelling	Inhealth Technologies Carpinteria, CA, USA	recessed hinged valve	silicone rubber	frontloading	Length: 6, 10, 14, 18, 22, 25 mm Ø: 6.75 mm

Curriculum vitae

De auteur van dit proefschrift werd op 2 februari 1965 geboren in Rotterdam. Na het behalen van het eindexamen VWO aan het City College In Rotterdam werd in 1984 begonnen met de studie Lichamelijke Opvoeding aan de Vrije Universiteit te Amsterdam. Na ingeloot te zijn werd in 1985 gestart met de studie Geneeskunde in Rotterdam. Het artsexamen werd in 1992 behaald. Van oktober 1992 tot januari 1994 werd de dienstplicht als arts bij de Koninklijke Marine vervuld. April 1994 werd als arts-assistent KNO begonnen op de afdeling KNO van het Academisch Ziekenhuis Groningen. Hier werd van 1 januari 1995 tot 1 januari 2000 de opleiding tot KNO-arts gevolgd. Van 1 januari 2000 tot 1 september 2000 was de auteur als staflid werkzaam aan deze kliniek. Thans werkt hij als KNO-arts in het Bosch Medicentrum in 's-Hertogenbosch. De auteur is getrouwd met Johanna Antonia Fransisca Walboomers en heeft twee kinderen: zoon Bram en dochter Willemijn.

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